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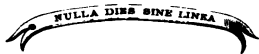
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The Hypodermic Syringe

BY

GEORGE L. SERVOSS, M. D.

Editor of "Nevada Medicine"

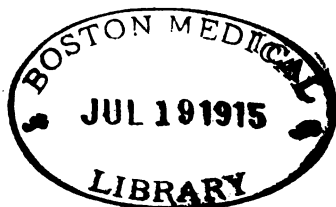
Member of the Nevada State Medical Association

Fellow of the American Medical Association

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GEORGE L. SERVOS, M. D.

Dedication.

TO THE MAN WHO TAUGHT ME THE
SECRETS OF HYPODERMIC MEDICATION

JOHN H. OLIVER, M. D.

IS THIS BOOK AFFECTIONATELY
DEDICATED.

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PREFACE.

It is now several years since Bartholow offered us his little work on Hypodermic Medication. This book has long been out of print and now is seemingly, after various attempts on our part to secure a copy, is out of the market as well. In the following pages it has not been the attempt of the author to inject anything of an original nature, but rather to give a condensed narrative of the hypodermic syringe and its possibilities, as set forth by numerous authors and investigators. It is very probable, in view of the wonderful strides made in hypodermic medication in recent years, that many omissions will be found. Without other apologies, we offer this little book.

George L. Servoss, M. D.

CHAPTER I.

Introduction.

Less than a century ago the hypodermic syringe and the hypodermic method of medication were first brought into use. Primarily, those who used the instrument, employed it for the quick introduction of morphine for the relief of pain and it became a common comment that he who used the instrument, did so for the purpose of administering this drug and no other. This idea lingers in the minds of many, even today.

However, with the passing of time, it was found that many other drugs might be exhibited in this way, and the hypodermic method paved the way for a greater and better drug application. Not only have been drug agents employed by this method, but it opened an avenue for the application of many substances which could not be administered orally, because of the destructive action of the digestive ferments of the alimentary canal.

Not only did this method allow of the rapid introduction of a drug into the system, but it was found, as time went on, that smaller doses were effective when administered in this man-

ner, because of the fact that all of the drug was absorbed, which was not always the case when drugs were exhibited by the mouth.

Many drugs, administered orally, brought about that condition known as idiosyncrasy, which was found not to be the case when the same were given hypodermically, and because of this fact it is very probable that many lives were saved through the use of the instrument.

Many drugs, such as iron which was invariably followed by constipation, when given by the mouth, gave undesirable results, were found to produce nothing of this sort when the hypodermic method was employed in their introduction. This fact undoubtedly has had more to do with the numerous advances in drug improvement than any other one thing, as the pharmacists and chemists have been working toward the end where it will be possible to administer every known drug, in one form or another, through the use of the hypodermic syringe.

To employ any drug agent by the hypodermic method, it must be pure, clean and readily absorbed, and for this reason, in order that drugs may be employed in this manner, the hypodermic syringe has been the means to the end whereby active agents have become the rule and not the exception. In the beginning there were but few drugs which could be employed in this manner; a few of the alkaloids, and even these, in the earlier days were far from pure. Recognizing the fact that only the

active principles of drugs could be employed by the hypodermic method, efforts were made to segregate and isolate such principles in their purest possible form, until today we find that the list of agents applicable in this manner are becoming legion. Many of the chemicals, which in their simple forms could not be so employed, have within recent years been offered in organic form and non-irritable, and today we see iron, arsenic and the mercurials in such form being employed to a very considerable extent by this method.

Primarily the hypodermic syringe was used to introduce remedial agents only beneath the skin, but as time went on it was found that, in many instances better action was obtained if the injections were thrown deeper into the muscular tissues, and still later the intravenous mode was adopted and the agent thrown directly into the blood-current. Still later the method of throwing drugs and other substances directly into the spinal cavity was introduced, and in some instances the instrument has been employed to throw therapeutic agents directly into the cerebral cavities, and into the cerebral meningeal cavities.

Some three decades ago cocaine was introduced and it was found that it was a local obtundant when applied to surfaces where absorption was possible. The hypodermic syringe allowed of its use in the obtunding of skin and deeper tissues, through the throwing of solutions of the drug beneath the surfaces by

means of the syringe. Thus was born local anesthesia and it was made possible through the hypodermic method, which would not have been possible otherwise. It also made possible spinal anesthesia, which followed shortly after that of a local nature.

While it is true, and more's the pity, that the hypodermic syringe has been blamable for the production of the drug habit in many, nevertheless, the fact that it has saved many more lives than it has cursed, makes the instrument one of the most valuable in the hands of the medical profession.

It is not, however, an instrument to be employed indiscriminately, and more especially when narcotic drugs are employed by this method. The person who employs it in such manner is guilty of a crime against humanity and, as a rule, is not a successful practitioner. It is an instrument only for emergencies, in the introduction of narcotics, and never should be employed otherwise than as such. The continued use of the narcotics is rarely indicated, and when such indications are met, drugs of this character are better administered orally, in that the patient may not become aware of the fact that habit forming drugs are being administered, as the moral effect of the agent may be greater than is the physical.

As has been said, the hypodermic method has paved the way toward a greater and better materia medica. Had it not been for the invention and introduction of the hypodermic

syringe it is very probable that many of our biological products, such as the antitoxins, bacterins or bacterial vaccines and substances of this character would never have been brought forth, as it is a known fact that many of these substances become inactive when exhibited by way of the alimentary canal, but are highly active when introduced subcutaneously, intravenously or thrown into the spinal cavity. In this way not only has the hypodermic syringe shortened disease, but in addition has lowered mortality to an astonishing extent.

The hypodermic has simplified anesthesia through the allowing of the introduction of obtunding drugs, both locally and generally and to such an extent that operative and post-operative shock have been practically obliterated. Local anesthesia has done away with the necessity of general anesthesia in many minor surgical operative procedures, and had it not been for the hypodermic syringe this could not have been possible.

Many diseases, considered incurable under the older methods of drug administration, are now showing either improvement or satisfactory termination when the hypodermic method is being employed. Because of this, and for various other reasons, the hypodermic method of drug administration has become a boon to humanity.

CHAPTER II.

The Syringe.

The instrument most commonly employed is a simple plunger pump consisting of a barrel, piston, rod, finger and thumb pieces and needle. Primarily a hard rubber syringe was employed to which a needle was attached. Later, an instrument with a glass barrel, with leather plunger was introduced. The objections to both the rubber and initial glass syringes, were that both were equipped with leather washers, which frequently, unless the instrument was used continuously, or given frequent attention, dried out, and at the moment when the syringe was most needed, it was found inactive as a pump, simply because of the fact that the looseness of the plunger and its lack of contact with the barrel allowed of no suction or propelling force. Endeavors to overcome this objection were made. In one instrument the piston rod was made hollow and filled with oil which was fed automatically to the plunger, thus keeping the latter soft and expanded, but this instrument had its objection in that too much of the lubricant was present at all times and that it was kept clean with

difficulty. In another instrument the piston rod was continued beyond the plunger and a nut applied below the second washer of the plunger, this nut being supplied with ribs or projections which fitted into corresponding depressions in the lower end of the barrel, thus allowing of tightening with a few turns of the rod, and acting to expand the washers through mechanical force. This instrument was superior to others of the leather washer type, but, unless the washers were kept moist, the mechanical force became ineffective because of the fact that pressure had no effect upon dry washers. Another objection to the leather washers was the fact that they were liable to disintegration and that particles of leather were carried into the needle to clog that portion of the instrument, or were thrown into the tissues to become possible irritants, or worse if the instrument were employed to introduce drugs intravenously, to act as foreign bodies in the circulation.

Later on asbestos, either in the shape of sheet washers, or cord wound about the piston, was substituted for leather, but it was found objectionable for many of the same reasons as was the leather plunger. It dried out and disintegrated. It had one superiority over leather; it could be kept clean with greater ease. Rubber was used as plunger and washer material, but with but little success, as any greasy lubricant caused rapid disintegration, and if the syringe were not lubricated it was operated

with difficulty, because of the tendency of the soft rubber to cling tightly to the barrel walls.

Recognizing the fact that a radical change must be made in the syringe, if it were to be invariably useful and effective, and under all conditions, the instrument makers introduced the all metal hypodermic. In this both barrel and plunger are of solid metal, the one being ground to accurately fit the other, thus giving a perfect contact and likewise perfect suction and propelling force. One objection to this instrument is the fact that, being supplied with a solid metal barrel, the operator cannot see just what he is doing, and if employing the instrument for the introduction of agents employed for the establishment of local anesthesia, is obliged to rely wholly upon the scale upon the piston rod in order to determine just how much of the solution is being introduced. This, however, is not a serious objection. Another objection lies in the fact that this instrument must be perfectly lubricated in order to have it perfectly effective in propelling and suction force, but this objection is overcome if aseptic greases, as petrolatum, are employed, but even then there is no absolute certainty that the instrument is aseptic at all times, as the upper portion thereof is not absolutely tight. However, this type of syringe may be rendered clean through boiling or the application of antiseptics. Care should be taken not to employ sublimate solutions for this purpose, excepting in emergencies, as the continued use

of this agent would eventually corrode both barrel and plunger, thus rendering the instrument imperfect through lack of contact between these portions. This type is, however, one of the most satisfactory we possess, as it overcomes the major portion of the objections offered to those before mentioned.

To overcome the objections to the all metal syringe, the glass barrel instrument, with solid steel plunger was introduced. In this instrument, instead of coming in direct contact with the barrel, the plunger was fitted tightly into a cork washer at the top of the barrel, and exerted suction and propulsion through air displacement. If the washer fitted the plunger snugly this instrument acted admirably, but if there were any deviation of contact it became worthless, as a vacuum was an impossibility. However, in point of cleanliness, this instrument was a distinct improvement over the others heretofore mentioned.

The Koch type, in which a soft rubber bulb at the top of the instrument produced suction and propulsion, had some superior points, but owing to the liability of disintegration of the bulb, with the necessity of frequent renewals, and also the fact that lack of contact between the bulb and barrel might occur, this type has not become greatly popular. It has, however, some advantage over the piston types. No lubrication is required and it is easily kept clean.

Following closely upon the trail of the glass and metal types appeared the all glass, or Luhr type, in which a solid glass plunger is accurately ground into the barrel, thus affording a perfect contact. This instrument has the advantage that lubricants are unnecessary, as the fluids employed allow of free action. This instrument may be kept absolutely clean, either by boiling or by treatment with any of the chemical antiseptics. In emergencies, when boiling is impossible, it may be rendered aseptic through the application of alcohol, phenol or immersion in sublimate solution, and this without the least fear of damage to the instrument. The only objection to the Luhr type is its friability and liability to breakage, and the fact that after use, especially with any of the salts, it must be thoroughly washed out, else these crystallize and cause the plunger to adhere to the inner sides of the barrel. Should this occur, boiling of the instrument becomes necessary. This fact should be remembered, lest the syringe be out of commission when needed in an emergency, and when time for cleaning might not be allowable.

Another type which is in use is that in which a metal plunger is employed with a glass barrel, the former being ground to accurately fit the latter. The main objection to this type is that it must be boiled to be rendered aseptic. It has the superiority over the all-metal syringe, in that the operator may see the contents of the barrel. This instrument is used

in instances when more than ordinary force is desired, as in the introduction of large quantities of fluids into the deeper muscular tissues, or where the obtunding effects of pressure are desirable.

In the original syringes there were numerous packing washers, usually of leather, and these, unless the instrument was kept in good condition, were liable to dry out and allow of leakage at either or both ends of the barrel, with consequent lack of proper suction and propulsion. Not infrequently did the operator find his instrument worthless after a long period of non-use, simply because of this drying out and shrinkage of the packing. The needle, in the earlier types, was threaded to a nipple at the lower end of the barrel, with an interposing washer to prevent leakage, and this, like all other washers had a tendency to dry out, and that very rapidly, thus allowing that which it was supposed to prevent, serious leakage.

With the introduction of the all metal type all of the washers employed as packing, with the exception of the one between the needle and barrel, were obliterated, although in some instances this objection was overcome by fitting the needle to the nipple by means of a slip, or friction, joint. In the all-glass barreled type the washers are practically all done away with, as they are unnecessary. The needle in these syringes is ground to accurately fit a ground nipple, the contact by cohesion

allowing of a practically tight joint, which under ordinary circumstances, does not leak.

Recently there has been introduced a new type. This consists of a collapsible, block-tin tube containing the drug in solution and ready for application, and to which the needle is permanently attached, the instrument being sealed by means of a wire passed through the needle. The latter is covered by a glass capsule, and being originally aseptic remains in such condition until used. Aside from additional expense, this type is ideal, in that cleanliness is practically assured and because of the fact that the instrument is used but once and then thrown away, overcoming any possible tendency to carry infection from one patient to another through carelessness.

Hypodermoclysis, or the throwing of large quantities of fluids into the subcutaneous tissues, is one of the outcomes of the hypodermic method. This operation, which requires slowness in introduction is carried out through the use of gravity, rather than syringe propulsion, the douche bag or can being the instrument employed, and the force graduated by the fall of the fluid. Gravity is also employed in the introduction of fluids into the spinal cavity.

CHAPTER III.

Technique.

Preparation of the Syringe—If the glass barreled syringe, either with leather, asbestos or rubber plunger is employed, it should be boiled and care should be taken to see that no bits of the plunger are in the solution used. If there is not time to thoroughly boil the instrument it may be rinsed, inside and out, with either 95 per cent. alcohol, or a solution of one of the chemical antiseptics, but it should be borne in mind that a corrosive sublimate solution may work havoc, through its attack upon the metal parts.

The all-metal type may be cleaned by boiling, or by the use of alcohol or chemical antiseptics, but care should be taken not to use bichloride, for fear of corrosion, which will, in time, interfere with the suction force.

The above remarks apply, in the main, to those instruments having glass barrels with metal plungers.

The all-glass type offers none of the objections or obstacles presented by those heretofore mentioned. Instruments of this type may be boiled, treated with alcohol, or immersed

in any of the solutions of chemical antiseptics, without fear of interference with the working of the instrument.

In any event, no matter what type of syringe is employed, it should invariably be rinsed thoroughly with sterile water prior to drawing up the drug carrying solution, as many of the antiseptic agents may prove irritant and cause more or less subsequent trouble.

In doing a hypodermoclysis, the fountain syringe, or tank, should be rendered thoroughly aseptic, in one way or another. The rubber bag and tubing may be boiled a few times without danger, but frequent boiling may cause disintegration of the material. The pouring of a hot solution of one of the chemical disinfectants through the bag and tube will usually suffice. With the metal or glass tank, boiling will render the receptacle aseptic, and as there is usually plenty of time for this procedure, it should be carried out in every instance.

Preparation of the Needle—It goes without saying that it is as important, if not more so, to have the needle as aseptic as is the body of the syringe. If a needle is properly cared for after each injection, and as is frequently the case, kept in alcohol when not in use, there need be but little fear of trouble or infection from a dirty needle. However, prior to use, and after attachment to the body of the syringe, the needle should be subjected to further attention. Immersion in 95 per cent. al-

cohol usually assures cleanliness, but in full strength tincture of iodine gives greater assurance that infection will not follow the wake of the use of the instrument. After receiving this treatment the needle should not be touched, in fact this latter treatment should be given just prior to its being plunged underneath the skin. In making deep puncture into the muscle many find that a needle dripping with iodine is never followed by abscess, or even irritation. After the application has been made, full strength alcohol should be drawn into the syringe and thrown out, and this repeated two or three times. If this is done the instrument will be perfectly cleaned and will also dry wholly and quickly. If this plan is followed it will not be necessary to keep a wire within the needle during the intervals of non-use, as its lumen will remain open.

Preparation of the Skin—As in all operations where the epidermis is to be broken, even though the puncture from the hypodermic needle is very slight, absolute cleanliness **must** be observed. When the smaller needles are used and but one application is to be made it may not be necessary to scrub the area, but some antiseptic should be applied. Some swab the surface with a 95 per cent. alcohol, with ether, or a solution of some chemical antiseptic. Today, with the recognition of the value of tincture of iodine in skin disinfection, it is probable that this agent gives us the best means whereby to guard against local infec-

tion, incident to the use of the hypodermic. In the use of this agent the site of puncture is painted over with a sufficiently strong solution of iodine in alcohol to warrant asepsis. When the skin is treated in this manner and a clean syringe and needle are used, there is but little chance of abscess formation. If a needle of large caliber is to be used, as is hypodermoclysis, it will be well to scrub the skin, as for a surgical operation, prior to the application of the iodine solution.

Methods of Hypodermic Administrations—

It goes without saying that all agents employed hypodermically must be in perfect solution, and in such condition as to be readily and rapidly absorbed, and that there must not be any foreign or solid matter present. The solution must also be sterile, else infection follow. Nor should, if it can be helped, the liquid injected be irritant.

When a single injection, of small quantity, is to be made, any portion of the skin surface may be selected as the site of operation. It was the habit at one time to pick up a fold of the skin between the thumb and forefinger of the left hand and to plunge the needle into the skin so picked up and some still follow this plan. This is not, however, a good procedure, as there is more or less liability of bruising of the tissues so picked up, with a possibility of resultant abscess. The needle may be easily introduced into the subcutaneous tissues without picking up the skin. Another method is

to plunge the needle deeply into the underlying muscular tissues. It is very probable that absorption takes place with greater rapidity from the subcutaneous than from the muscular tissues, although from either method good results have obtained. Where slower absorption is desired, as in the administration of salvarsan, the intramuscular method is undoubtedly preferable. The skin of the forearm is usually the site of the single injection.

When several injections are to be made, as in the administration of iron cacodylate, and other agents of this character, the preferable site is in the tissues below and to the right of the left scapula. There is an abundance of cellular tissue at this point and the skin and surrounding tissues not being highly organized and sensitive, but little, if any, discomfort is experienced by the patient, even though numerous injections may be given. Absorption takes place readily from this particular site, and this should be remembered when the bacterins and antitoxins are to be administered.

In performing a hypodermoclysis the needle should be of large caliber and introduced at a point where there is considerable cellular tissue, as large amounts of fluids are usually employed and must be thrown where they may have the greatest room and at the same time be absorbed rapidly. The abdominal and chest walls are the usual sites selected, although a good location is beneath the left scapula.

When using the hypodermic for intravenous injections scrupulous cleanliness must be observed at every step. One of the veins of the arm is usually the accepted site. The skin should be prepared as for surgical operation and the instrument rendered thoroughly aseptic. The operator, as regards his own person, should be as careful as in a major surgical operation. Care should be taken to see that the solution employed is perfect, sterile, and carries no solids, **absolutely**. The vein is rendered prominent by tourniquet, not sufficiently tight to totally obliterate the circulation completely and the vein is either cut down upon and exposed, or the needle is plunged through skin, subdermal tissues and vein wall. The latter method is preferable, if possible, and it usually is. After the injection the resulting puncture is covered with a drop of collodion, or painted with tincture of iodine. If an incision has been required the resulting wound is treated as is any other surgical incision. The treatment of the puncture is usually necessary in intravenous injections because of the fact that a needle of considerable caliber is usually employed.

In making the puncture, either subdermally or intramuscularly, the needle should be introduced with a quick thrust, and withdrawn slowly, introducing the fluid as withdrawal is being made. In this way the fluid is distributed over a larger area and gives less discomfort to the patient, besides offering greater

ease of absorption. Either in the subcutaneous or intramuscular method the needle should be plunged to its full length before any of the fluid is thrown from the syringe.

In making injections into the spinal cavity a measured amount of the spinal fluid should be withdrawn and a like amount of the solution used injected. It goes without saying that spinal injection should be made with the greatest efforts toward asepsis.

The antitoxins, bacterins, tuberculins and other biologic products should be injected at such points as favor the greatest rapidity of absorption. The methods in this connection will be considered at greater length in those pages in which the biologic products will receive especial attention.

CHAPTER IV.

Remedies.

During the earlier days of hypodermic medication it was suspected that morphine was to be employed with every production of the syringe, and to a certain extent this idea prevails today in a vast majority of instances. This is not, however, the truth at this time, as the number of other agents so exhibited might be said to be legion. In fact it might be said that the practice of medicine could be carried on successfully without administering more than a few drugs, or other agents, orally.

Not only are the chemical drugs and the alkaloids of plants so employed, but some of the whole plant products as well. We find the eclectics injecting considerable quantities of fluid lobelia hypodermically, and ergot, in aqueous extract, has been so employed.

With the discovery of diphtheria antitoxin the value of the hypodermic syringe was increased manyfold, as it paved the way for the introduction of numerous other biologic products. Not only has the hypodermic become an absolute necessity in the exhibition of the biologic products, but likewise in the

administration of many drugs either wholly or partially inactive when introduced via the alimentary canal.

The method allows of the application of the majority of the alkaloids, as well as many of the other active principles and concentrations of plant drugs, and not only does it assure of prompt reaction, but in addition practically gives an absolute assurance of full drug effect in every instance, as none of the agent is lost through lack of absorption, as is so frequently the case following oral exhibition.

In the earlier days of hypodermic medication stock solutions of the drugs employed were kept on hand. While they may have been active when freshly prepared, they like all fluid mixtures were liable of deterioration, and to become foul. Abscesses occurred to a greater or less extent when such solutions were used, and it was due undoubtedly to a large extent, to their unclean condition. With the establishment of the manufacturing pharmacist and the introduction of tablet triturates, those drugs to be employed hypodermically were offered in such form, each tablet carrying the average dose of the drug to be employed. This not only gave a greater assurance of cleanliness, but an absolute assurance of uniform dosage. In the beginning only a few of the alkaloids, such as morphine, strychnine, atropine, etc., were made, but with the recognition that many other agents were applicable in this manner the list grew to one

of large dimensions, and is still receiving additions so rapidly that one is obliged to give the matter daily study to be down-to-date.

Among the drug and chemical agents employed and listed at present we find the following in tablet form, either alone or in combinations:

Aconitine
Apomorphine
Aspidospermine
Atropine
Cactin
Caffeine
Cocaine
Codeine
Colechicine
Condurangin
Digitalin
Ergotin
Eucaïne
Gelseminine
Heroin
Corrosive Sublimate
Hyoscine
Hyoscyamine
Mercury Succimide
Morphine
Nitroglycerine
Nuclein
Physostigmine
Pilocarpine
Picrotoxin

Quinine and Urea Hydrochloride
Scopolamine
Sparteine
Strychnine

Numerous combinations are offered in which the above list of drugs figure, but it is not necessary to mention them in these pages. Nor is it necessary to give the list of hypodermic solutions, as these are employed but seldom, usually in institutions, if at all, and rarely there.

Many chemicals and other drugs are now offered in sterile solution in hermetically sealed ampules, especially the cacodylates of iron and sodium, as well as of mercury, several of the mercurials, camphorated oil, ergot, strophanthin and many other products, a list too long to be given space in these pages, and one which is still far from being complete, as additions are being made daily thereto. The ampules, like the tablet triturates, represent the average adult dose. Among the advantages of the ampule are that the contents is prepared and ready for use, a uniform amount of the drug is offered and that the solution is clean and sterile.

In the treatment of specific infectious diseases the following antitoxins and serums are employed, and are offered in specified units of dosage in aseptic syringes, as a rule:

Diphtheria Antitoxin
Tetanus Antitoxin
Anti-Dysenteric Serum
Anti-Pneumococcic Serum
Anti-Streptococcic Serum
Antimeningitis Serum

In the treatment of infections, both as a prophylactic and after the infection has been established, the bacterins, or bacterial vaccines, suggested by Wright and others, are found very effective. These are obtained either in aseptic syringes, each representing a single dose, or in ampules containing several doses. They are as follows:

Acne-Bacterin
Coli-Bacterin
Friedlander-Bacterin
Neisser-Bacterin (Gonococcus Vaccine)
Neisser-Bacterin Mixed
Cholera-Bacterin
Diphtheria-Bacterin
Influenza-Bacterin Mixed
Meningo-Bacterin
Neoformans-Bacterin
Plague-Bacterin
Pneumo-Bacterin
Pneumo-Bacterin
Pulmonary Bacterin Mixed
Pyocyano-Bacterin
Scarlatina-Bacterin
Scarlatina Bacterin Immunizing
Staphylo-Bacterin

Staphylo-Acne Bacterin
Staphylo-Albus Bacterin
Staphylo-Aureus Bacterin
Staphylo-Bacterin Mixed
Staphylo-Strepto-Bacterin Mixed
Strepto-Bacterin
Typho-Bacterin
Typho-Bacterin Immunizing
Typho-Bacterin Mixed.

Normal Horse Serum, the Tuberculins and other biologic products are employed hypodermically, as well as otherwise.

The hypodermic has made possible many special drugs and chemicals which would not be of worth otherwise, or at least, only slightly so. Among those recently introduced, and one which has been employed to a very considerable extent is arsenobenzol, or salvarsan.

In the following chapters an effort will be made to give a full history, with application, of practically all agents employed hypodermically.

CHAPTER V.

Drugs and Chemicals.

Apomorphine—Internally, apomorphine is employed as an expectorant and hypnotic, while hypodermically its chief office is that of an emetic, and it is for this effect that the drug is employed by the latter method. It is by far the best emetic we possess, when prompt reaction is desirable. The emetic dose, hypodermically is from 1-20 to 1-10 grain, based upon the age and condition of the patient. The fact that it is purely emetic and produces very little, if any subsequent nausea, makes it doubly valuable. It is employed in emptying the stomach in poisoning and suffocation, to relieve an overloaded stomach, or that of the alcoholic in delirium tremens or to dislodge foreign bodies from the throat or esophagus. It is likewise useful in the treatment of spasm and of hysteria.

It should be remembered that apomorphine in itself, has more or less depressing action, and in marked narcosis it should be employed with care, lest it increase the condition. In opium poisoning, where the narcosis is very deep, it is preferable to employ other emetic

than this. This likewise applies in some cases of alcoholism. The condition of the patient should be considered at all times and the drug employed accordingly.

The application is made either subcutaneously or intramuscularly, as preferred, or as the conditions permit. In either instance the reaction is usually prompt and the physician and nurse should be prepared, prior to making the injection, with vessels ready to catch the vomit. The operator, should by preference, stand behind his patient, or to one side, as unpleasant accidents have occurred through the almost immediate action of the drug. Apomorphine gains its effect through central nerve action, and not through direct gastric contact, which accounts for its very mild or non-emetic effect when administered orally.

Properly administered, with the conditions under consideration at all times, this agent is one of great value; in fact, in numerous instances, has proven a life saver, but it should be administered only when indicated.

Atropine—It is probable that no other single drug offers the wide range of possibilities that does atropine. It is equally active both internally and subcutaneously, although for immediate effect the latter mode of exhibition is the preferable one. As a rule, when exhibited hypodermically, it is for a specific purpose, and the full dosage is used.

Atropine is the basis of all secret cures for alcoholism, the fullness of the head which it

produces rendering the liquor effect disagreeable.

Aphonia of the hysteric form is relieved by full doses.

Atropine is of use in asthma with cool, moist skin and loose sputa.

It sedates bladder irritability and checks nocturnal enuresis.

In bronchitis it checks the bronchorrhea, with profuse flow of mucus, and relieves the irritative cough.

A full dose acts to relieve spasm due to both billiary and renal calculi, eases the pain and allows of the passage of the stone.

Given to effect, it will abort acute nasal catarrh and dry up the secretions. In this connection it may be given orally in broken doses to effect, or hypodermically in like manner.

It increases the cerebral blood-supply for the time being and is temporarily of use in cerebral anemia, but by determining the blood to the surfaces is of probably greater use, in full dose, in cerebral congestion.

In Asiatic cholera, cholera infantum and cholera morbus, through directly opposing irritation of the vagus, it relieves cramps, pain and diarrhea. It likewise relieves the same symptoms in intestinal colic and is the best remedy in lead colic.

Atropine is of use in combatting convulsions due to congestion, teething or whooping-cough, and allays irritation and overcomes cough,

spasmodic, sympathetic, nervous or asthmatic in form, and relieves irritation and stimulates respiration in croup.

Through relieving irritability, it is useful in cystitis, especially the form due to "catching cold," which it acts to abort.

It relieves the cerebral anemia in simple delirium; is useful in delirium tremens with insomnia, cyanosis, cold skin and coma vigil, and to stimulate cerebral circulation and relieve insomnia in dementia.

Atropine is useful during the sweating stage of dengue, if excessive or weakening and serves to check the excessive flow of urine in diabetes insipidus, and to check the excessive flow in diarrheas.

It aborts exudation in diphtheria and is of value to support the heart during the acute inflammation of throat and tonsils in this disease.

Atropine relieves the spasmodic and neuralgic forms of dysmenorrhea, with dark fetid discharge and crampy pains and chills and is the best hemostatic in menorrhagia, as well as in puerperal hemorrhage, and is the best remedy for ovarian neuralgia. It seems to have a selective action upon the pelvic organs, as a whole, of the female.

In dyspepsia it serves to check hyperchlorhydria, to relieve gastralgia and overcome constipation through the paralysis of inhibition.

Through overcoming spasm it is of value in all forms of dyspnea, consequently its useful-

ness in asthma and other involvements of the air passages with this as a symptom.

It is useful in fevers to bring about delayed eruptions, for insomnia and low delirium, photophobia, hebetude, hemorrhages and to sustain the heart.

In gastric conditions it relieves neuralgic pains of simple gastralgia, and stops the pain and vomiting of gastric ulcer and checks the production of acid. It is useful in stomach pains in gout.

To dry up the secretions it would seem indicated in edema of the glottis, as well as in other edemas.

As in acute nasal catarrh, atropine is indicated in hay fever to dry up the secretions. As a rule its action is only temporary in this condition.

Atropine is useful in many forms of headache. It breaks up the attacks in excessive meat eaters, and is useful for pain over the eye, for photophobia, intolerance of noise or motion, those forms due to uterine or gastric irritation in young women and in those cases where the headache is accompanied by pale face and shrunken skin, with pulse small and contracted.

It relieves the irregular rhythm and cardiac strain in heart disease.

In hemorrhages of all sorts, as hematemesis, hemoptysis, hemophilia, rectal and puerperal, and the bleeding of hemorrhoids and to relax spasmodic sphincter in the latter, atropine is

of great value. In all forms of internal hemorrhages its indications are marked. It acts by determining the blood to the surfaces, and for this reason, is likewise indicated in all internal congestions.

Through bringing about relaxation, full doses may overcome strangulation in hernia.

It will relieve the pain in herpes zoster.

Combined with strychnine to steady the nerves, full doses will relieve the spasm in hic-cough.

In hypochondria, for cerebral anemia, general relaxation and sexual atony and in hysteria, for convulsions, aphonia and the puerperal form, and to strengthen the erection and relieve nervous dread in impotence.

In acute attacks of influenza for the headache, and to overcome excessive sweating and to dry up other secretions, as in acute nasal catarrh.

It is useful in insomnia due to prostration, low arterial tension, with contracted pupils and frontal headache and to those forms due to eyestrain.

It may relieve intestinal obstruction through relaxation of spasm and relief of pain.

During labor it stimulates uterine contractions and lessens pain and tendency to hemorrhage, and during lactation is useful in decreasing over-flow of milk. It is useful in mastitis.

Atropine is useful in most of the nervous

conditions, as laryngismus stridulus, locomotor ataxia, etc., in overcoming paroxysms.

It may, in full dose, abort attacks of both lumbago and sciatica and should be given trial in both conditions, invariably by hypodermic, and at the seat of the pain.

In mania it allays irritation, induces sleep and quiets delirium, and is indicated in nymphomania, hypochondria, delusions of persecution, and whenever it is desirable to stimulate the cerebral circulation. It relieves the constipation and low arterial tension in melancholy.

It brings out delayed eruptions in the eruptive fevers, and is indicated to combat the depressed vital powers and low temperature in measles and in the sore throat of scarlatina.

Atropine overcomes the pain and irritation in acute nephritis.

A single full dose may abort attacks of neuralgia. It is indicated in the various forms, as sciatica, lumbago, uterine, ovarian, intercostal, myalgia, gastralgia, tic, dysmenorrheal, and in spinal irritation. In otalgia in children with coryza.

For the perspiration of an excessive nature in phthisis and other diseases, atropine usually gives prompt relief and is indicated in all conditions of this sort.

As in acute inflammation of the nasal passages, atropine is indicated to abort acute pharyngitis and to dry up secretions thereof, as well as to relieve the pain and fever.

In phthisis it not only acts to check sweating, but relieves diarrhea and bronchorrhea, irritative cough and dyspnea.

Theoretically, it should be indicated as an abortive agent in the initial stages of pneumonia, if given to full effect. It must, however, be administered early to have such effect, if this is a possibility.

In scurvy and all other conditions with excessive action of salivary glands, atropine is of great value as a corrective and to limit the secretion. It likewise overcomes the relaxation in scurvy.

It has been employed with some success in seasickness, and is said to prevent attacks if given after bowels are thoroughly emptied.

Atropine is indicated in local muscular spasm of sphincter and in those spasmodic conditions due to hysteria, anemia and teething.

For relaxed genitals, nocturnal emissions and lack of orgasm in spermatorrhea.

In all cases of heat exhaustion, with low arterial tension.

It is frequently a "life saver" in syncope and collapse, and is given after initial doses of nitroglycerine to prolong the cerebral hyperemia.

It is said to be of value, when injected close to the wound, in tetanus.

In tonsillitis, as in other inflammations of that neighborhood, if given early, will abort the attack. It must be given to effect, or until

the throat feels dry, in order to gain such effect.

Atropine is indicated in typhoid fever with contracted pupils, low muttering delirium and weak heart, and in varicla with low muttering delirium, prostration and delayed eruption.

It is recommended for the neurotic vomiting of pregnancy.

These are only a few of the indications for atropine. It is **the one drug** worthy of great study as to its therapeutic possibilities.

The dose of atropine hypodermically is from 1-150 to 1-50 grain.

Aspidospermine—From quebracho. Aspidospermine is indicated in the dyspnea of asthma, emphysema and other respiratory maladies, but is less useful in the dyspnea of pulmonary tuberculosis. It is also mentioned as an antipyretic in fevers and to stimulate respiratory action. It is said to stimulate respiratory function and allow of greater endurance of physical action, as hill climbing. Shoemaker says that it acts admirably to relieve cyanosis and in acute rheumatism and in acute serous inflammations, to sedate the pulse and lower the fever. Lawrence reports a case of double pneumonia in a child in which he says that it showed a decided improvement in the breathing and heart-action.

In the treatment of asthma it is given in combination with morphine, pilocarpine and emetine.

The hypodermic dose recommended is about 1-20 grain, although larger doses have been given.

Aconitine—There are a few who rashly employ aconitine hypodermically, but those who have made a close study of this agent, say that this method should **never be employed**. The action of the drug orally administered is so prompt as not to warrant its use otherwise, and there are but few, if any, indications requiring greater promptness of action than is shown when the agent is given internally. It is mentioned in passing to emphasize this fact.

Cactin—Cactoid—Cactina—Cactine—A concentration from *cactus grandiflorus*. There is a wide diversity of opinion relative to the usefulness of this product. These who have made laboratory experiments upon healthy animals say that it is wholly inactive, while those who have observed it clinically, in its action in sick humans, insist that it is a cardiac stimulant and tonic. Basing the use of the drug on the latter observations, it is well to give it consideration. It is said to gain its effect through increasing the nutrition of the heart. At any rate, in the face of many clinical observations and reports, and despite the adverse laboratory claims, it should be tried in those cases where such an agent is indicated. The dose is from 1-128 to 1-64 grain.

Caffeine—The alkaloid of coffee, tea and several other allied plants. In small dose

caffeine stimulates the heart and raises arterial tension and also stimulates cerebral function through additional blood carried to the brain. It also stimulates respiration and increases the urinary flow. This drug is useful in those conditions where it is desirable to stimulate the functions mentioned, but care should be taken not to over-dose, in that reverse effect may follow, as large doses are followed more or less, by depression. Caffeine is of great use in heart failure; also in dropsies with low arterial tension. The hypodermic dose is from 1-2 to 1 grain.

Cocaine—This drug will be considered at greater length under a special chapter on local anesthesia.

Codeine—This alkaloid of opium, with its salts, needs but little discussion, as its actions and uses are well known. As a sedative and antispasmodic, it is superior, in many ways, to its sister alkaloid, morphine. It does not so seriously impound the secretions, as does morphine, nor does it have the same paralyzing effect on the bowel. It is claimed that its use is not, as a rule, even though continued over a considerable time, followed by habit formation, but this has not been proved, and consequently it should not, as is the case with all opiates, be administered continuously with the thought that it is harmless in this particular. Codeine may be employed in practically all conditions in which morphine is indicated. It

is indicated in the relief of pain, spasm and as a hypnotic. It is said to be of value in the treatment of diabetes mellitus instead of the whole drug opium. The dose of the sulphate hypodermically, and also of the phosphate is from 1-4 to 1-2 grain.

Colchicine—The alkaloid of colchicum. This remedy is usually administered orally and for slow and continued effect, but where it is desirable to rapidly increase the eliminating function of the intestinal glands, liver, kidneys and skin, it may be given in full dose of 1-30 grain hypodermically. This is a very valuable agent in toxemias of numerous varieties, in that it favors prompt elimination of the toxins stored within the blood and tissues. It is indicated in rheumatism, gout; in fact in all toxic conditions, due to faulty elimination.

CHAPTER VI.

Drugs and Chemicals

(Continued)

Condurangin—While this agent has been recommended for the cure of cancer, especially that of gastric variety, the results attending its use have not been such as to warrant its use, as a cure. It does, however, in full dose relieve the pain of both gastric cancer and ulcer, and is said to have been curative in several cases of the latter, after having been employed over a considerable time. As its action is purely local it must be exhibited hypodermically in external cancers. The hypodermic dose is given as 1-64 grain.

Digitalin—While digitalis and all of its various products are invariably slow of effect, as a rule, it is claimed that the Germanic digitalin, administered in full dosage, gives a more or less rapid action, when exhibited hypodermically. As all digitalis products act to a greater or less extent as gastric irritants, it is possible that digitalin may be administered, hypodermically, in the face of such irritation, with success. For rapid cardiac stimulation it is probable that other agents are far more

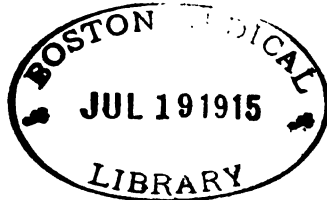
effective. The hypodermic dose is given as from 1-64 to 1-12 grain. The indications for the use of digitalis are too well-known to require attention in these pages. There are a number of other digitalis products manufactured for hypodermic use, each claiming superiority in one way or another.

Emetine Hydrochloride.—This drug is one of the latest drugs to be employed hypodermically. Dr. Leonard Rogers of Calcutta, after employing it instead of the whole drug, ipecac, gave two reports of his findings in its application in the treatment of amebic dysentery. These appeared in *The British Medical Journal* in 1912, June 22 and August 24. Even though patients were practically moribund when treatment was instituted, satisfactory results, with recovery followed. He also found that the drug in this form could be exhibited without the nausea and vomiting incident to the use of ipecac; that is, when the agent was employed hypodermically. There were, of course, some failures reported, but in the main the treatment was an improvement on all others hitherto employed. Since the initial reports made by Rogers, several other writers have reported like results. The description of the use of emetine hydrochloride, as given by Rogers is as follows: "I began with one-third grain doses, equal to 30 grains of ipecachuana, but now use half or two-third-grain doses in adults, while one-third of a grain may be given

with perfect safety in children of about eight years of age. I have several times given as much as a grain at once two or even three times a day in adults, and have never seen any depression or other alarming symptoms follow its use. Very occasionally severe pain may result at the seat of injection, but this is quite exceptional, and there is usually no sign of any local reaction. Half a grain twice a day gives uniformly good results, or a larger dose once a day may be used if this is more convenient."

This drug is also employed in hepatic abscess with good results, such abscesses being due to the ameba of dysentery. It is probable, as time goes on that emetine will be found of use in other intestinal disturbances. Emetine is suggested, instead of ipecac, in the treatment of hemoptysis of tuberculosis, and several French authorities, among them Chauffard, Dopter, Rouget and Dufour have reported successes in this connection. Emetine, by the mouth, is recognized as having quite a wide range of application and it is possible that it will meet like indication when applied hypodermically. It is a drug well worth studying.

Ergotin—Ergotoid (Liquid)—This extract of ergot has the same range of usefulness as have other forms of the drug, and that is rather a wide one. It is useful whenever it is desirable to stimulate non-striated muscle fiber. It acts to constrict the blood vessels



and consequently is useful, either alone or in combination with atropine, in the treatment of internal hemorrhages. It is indicated in congestions, especially cerebral of chronic form, and has been employed with good effect in epilepsy. It acts to overcome night sweats and has been found of use in whooping-cough. The particular variety of the product employed should have attention, as there are a number of different sorts marketed, and the dose varies to a very considerable extent. One particular sort should be accepted and employed to the exclusion of all others. Aqueous extracts are also employed hypodermically. As the dose varies, in the different sorts, to such an extent, none will be mentioned at this time.

Eucaïne—This product will be given consideration in the chapter devoted to local anesthesia.

Crotalin—The venom of the rattle snake. Is advised in epilepsy, but reports are meager and its use is not general.

Gelseminine Hydrobromide—This salt of the alkaloid gelsemium is being employed to succeed morphine in numerous instances and more especially in those cases where there is spinal irritation. It is a marked antispasmodic and being relieved of its tetanic associate, gelsemin, gives very reliable effect. The isolation and segregation of gelseminine has at last placed gelsemium among the list of worthy drug agents. Gelseminine is indicated in all fevers with

nervous tension, bright eyes and flushed face. It exerts its action largely through the spinal cord. This agent should be given a trial, instead of morphine, when the latter is indicated. The hypodermic dose of the hydrobromide is given as 1-50 grain.

Heroin—While heroin is listed among the hypodermic agents by many of the makers of pharmaceuticals, we question its desirability in this connection. It is a drug which is more or less uncertain in effect, and even small doses may be followed by symptoms of opium poisoning. Codeine fills all of the indications of heroin and in our mind, is far safer. If employed at all, the action of heroin should be watched very closely, the patient being under the eye of the doctor or nurse at all times, and with antidotes at hand for prompt administration. The dose of the hydrochloride salt is given as from 1-24 to 1-6 grain.

Corrosive Sublimate—This will be considered, with other mercurials, in a special chapter.

Hyoscine—It is probable that we have no better drug hypnotic at our command than hyoscine. It is likewise an admirable sedative and to some slight extent, antispasmodic. It acts to produce a practically normal slumber, and that within a very short time after its administration. A dose of 1-100 grain of the hydrobromide salt is usually followed by sleep lasting several hours, from which the patient

awakens as from normal slumber, refreshed. Hyoscine is superior in every way as a hypnotic, to morphine, or in fact any of the other opiates, in that it does not interfere with the eliminative functions. It also has the advantage that it may be administered over a long period **without the least tendency to habit formation**, the patient being able to drop it immediately and entirely when there are no further indications for its use. Combined with morphine, and administered prior to volatile anesthetics, it acts admirably to obtund the sensibilities of the patient and, subsequent to operation, assure him several hours peaceful slumber. In this connection, hyoscine will be given greater consideration in a succeeding chapter.

Hyoscyamine—Hyoscyamine is the sister alkaloid of hyoscine, from henbane. It is only mildly hypnotic but is markedly antispasmodic. As a rule it acts with considerable rapidity when administered orally, and to such an extent as to render it hardly necessary of hypodermic exhibition. However, if it is desirable, it may be employed by the latter method. As an antispasmodic, hyoscyamine is preferable to opium or any of its alkaloids. It does not interfere with elimination; in fact, in some cases rather favors such function, and more especially when spasm is the interfering factor. Orally, in combination with nitroglycerine, it acts with considerable rapidity, sufficiently so

under ordinary circumstances as not to require its hypodermic use. The dose of hyoscyamine sulphate is given as from 1-100 to 1-60 grain.

Mercury Succinimide—This salt of mercury will be considered in a chapter devoted to the various mercurials.

Morphine—Being so well known, morphine needs but little discussion in these pages. It was the first drug to be employed to any great extent hypodermically, and it has really established a bad reputation for this method of drug application, as he who employs the hypodermic syringe under ordinary circumstances is invariably suspected of using this particular drug. Morphine has really made many unscientific physicians. This drug has its place, and when properly employed, is of great value, but as a rule we possess other agents which are preferable in all ways. Morphine acts to destroy function, and especially of elimination, to a considerable extent, and consequently favors toxemia. However, in emergency its use should not be refused. The dose, hypodermically, is from 1-8 to 1-4 grain.

Nitroglycerine — Glonoin — Trinitrin — Although the action of nitroglycerine is very rapid when absorbed from the buccal mucous membranes, probably more so than when exhibited hypodermically, there are instances when the drug must be employed by the latter method. This is true when a patient is in syncope, or unconscious. The drug acts to stimu-

late the heart through dilatation of the capillaries and relieving the overburdened cardiac organ. It also acts to overcome syncope through the allowance of greater quantities of blood to the brain. As an initial remedy in the treatment of collapse, it paves the way to atropin, the latter maintaining the effect of the glonoin. It likewise acts well in combination with hyoscyamine to relieve spasm. Nitroglycerine is effective in the treatment of spasm due to congestion, especially of the internal organs, and acts as a synergist to the truer antispasmodics. When administered according to marked and recognized indications, nitroglycerine is a very valuable "life saver." The dose ranges from 1-500 to 1-50 grain.

Nuclein—The theory for the use of nuclein is that it reinforces the white blood-cells and increases their force to combat with infective agents. Whether or not this is true, it is seen that improvement follows its exhibition in some infections. There are reports of marked improvement following its intravenous application in pulmonary tuberculosis. It is an agent which should be employed upon theory in all infections, and more especially in those with little or no leucocytosis. The dose ranges as high as 60 min. intravenously. This agent, in any amount, seems harmless.

Physostigmine (Eserine)—Eserine increases peristalsis and relieves flatulence. It is employed hypodermically where, for one reason

or another, the oral exhibition is prohibited. Small doses increase arterial tension. The hypodermic dose is given as from 1-100 to 1-50 grain of the salicylate.

Picrotoxin—The active principle of fish berry. Relieves the night sweats in phthisis. Is also useful in paresis, nervous debility, chorea and paralysis agitans and may be applied in epilepsy. Has some of the actions of physostigmine, but does not cause nerve irritation. The hypodermic dose is 1-50 grain.

Pilocarpine—This alkaloid of jaborandi is our most powerful and rapid sudorific. For prompt depletion, it is indicated in edemas and dropsies. A full dose of from 1-10 to 1-5 grain of the nitrate, hypodermically, may save life in edema of the glottis, when all other remedies would undoubtedly show failure. In using pilocarpine it should be remembered that the remedy is a most powerful depressant, hence the subject for treatment should be studied carefully, prior to any application of the agent being made. In dropsies, where other than very prompt action is desired, it is probable that apocynin is preferable to pilocarpine. However, under the proper indications, pilocarpine is the drug parexcellence, and its use should not be refused at such times. The dose, hypodermically, is from 1-12 to 1-6 grain.

Quinine and Urea—This combination will be given consideration in a chapter devoted to local anesthesia.

Scopolamine—The actions of scopolamine are practically identical with those of hyoscine, and it is employed instead of the latter by some. We believe that a chemically pure hyoscine is the preferable agent when either is indicated. The dose is the same as of hyoscine.

Sparteine—An alkaloid from broom. Sparteine acts with rapidity, manifesting its effect within fifteen to twenty minutes; augments the heart energy; induces regularity of cardiac action; has no appreciable effect upon the blood-pressure. Germain See says of sparteine sulphate that it: "1.—It relieves the heart and pulse. It has a tonic action infinitely more marked, more prompt and more permanent than digitalis. 2.—It has an immediate regularizing effect upon the rhythm of a troubled heart. 3.—It accelerates the movement of the heart." It is valuable in mitral lesions and where the cardiac action is weak and irregular. It is particularly indicated in tobacco heart, exophthalmic goiter and rheumatic heart. It is preferable to digitalin when quick effect is desired. It is useful in the reduction of cardiac dropsies. It is eliminated by the kidneys with comparative rapidity and has but little if any tendency to accumulation. The dose of the sulphate is from 1-8 to 1-2 grain.

Strychnine—This alkaloid of *nux vomica* is so well known that nothing that could be said in these pages would add to the knowledge of

a single reader. It should, however, be given only when indicated, as it is an agent which is subject to more or less abuse. It should be remembered that strychnine is a good synergist in combination with the antispasmodics, through its ability to increase function. Like trinitrin, we should never be without it.

Veratrine—While veratrine is more or less irritant, when employed hypodermically, it is indicated under certain conditions. In puerperal eclampsia it is a very valuable remedy and should be pushed to full effect. In pneumonia and other inflammations, where the elimination is being interfered with, veratrine, in that it serves to rapidly flush the capillaries, is the indicated remedy. As it is very rapid of action when administered orally, in small quantities and at frequent intervals, unless the patient is unconscious or delirious this mode, in the majority of instances, is preferable. The hypodermic dose of the hydrochloride salt is given as 1-64 grain.

As the alkaloids are studied many others will undoubtedly be found eligible for hypodermic use, and as time goes on it is very probable that this method of drug exhibition will be employed, practically to the exclusion of all others. The agents above mentioned are only those which are more commonly in use at the present time, in so far as the active principles of plant drugs are concerned.

CHAPTER VII.

Mercurials.

At the present time we find many of the salts of mercury employed in the treatment of syphilis, as well as other diseases, by the hypodermic method. While it will not be our attempt to go into detail relative to the applications of these various salts, the dose and application, in brief, of each will be given. Reference is made to Merck's Index, 1907, relative to this class of chemicals.

Mercury Aminopropionate (Mercury Alanin)—Alterative and antisyphilitic. Hypodermic dose 1-12 to 1-6 grain.

Mercury Anilate—Antisyphilitic. Injected intramuscularly in 30—35 per cent. suspension in petrolatum.

Mercury Asparaginate—Used in treatment of syphilis. Hypodermic dose 1-12 to 1-6 grain per day.

Mercury Benzoate (Mercuric)—Used in syphilis and skin diseases. Merck gives the hypodermic dose as follows: 15m 1 c.c. of solution of 0.25 mercury benzoate, 0.25 sodium chloride, and 30 water, per day.

Mercury Bichloride—Used in syphilis, chronic rheumatism and skin diseases. Merck gives the following formula for making up a solution for hypodermic use:

Mercuric Chloride	0.1 Gm.
Sodium Chloride	1. Gm.
Water	100. C. C.

M. Sig. Use 8 to 15m for each injection.

Mercury Cacodylate (Mercuric)—Used in syphilis and was claimed at one time to be a specific and rapid cure. The dose for intramuscular injection is 1-2 grain per day.

Mercury Cyanide (Mercuric)—Used instead of the bichloride and said to be less irritating. Indicated in syphilis, diphtheria and membranous croup. The hypodermic dose is given as 1-12 grain.

Mercury Diodosalicylate (Mercuric)—Used in syphilis. Applied intramuscularly in 10 per cent. suspension in liquid petrolatum.

Mercury Ethylchloride—Used instead of mercuric chloride as an injection, and in the same indications.

Mercury Glycocholate—Indicated in syphilis. Made up in stable solution, the dose of which is 8 to 15m every second day. This represents 1-12 to 1-6 grain of mercuric oxide.

Mercury Iodate (Mercuric)—Antisymphilitic. Subcutaneous dose 1-6 to 1-4 grain every 2nd or 4th day.

Mercury Lactate (Mercurous)—Indicated in syphilis. Hypodermic dose 15m of a 1 per cent. solution daily.

Mercury Oxide Yellow (Mercuric)—Antisyphilitic. Exhibited intramuscularly, every 8 days, 1 c.c. of suspension of 1:30 in olive oil.

Mercury Resorcinolacetate—Antisyphilitic. Merck gives the method of hypodermic administration as follows: 3m of a solution of 85 grains of the salt in 85 grains of liquid paraffin and 30 grains of anhydrous lanolin, twice weekly, the mixture to be warmed to 25°C. before use.

Mercury Salicylate (Basic Mercuric)—Antisyphilitic, antigonorrheal, alterative. Hypodermic dose 1-3 grain, and maximum dose per day, 1 grain.

Mercury Succinimide (Mercuric)—Antisyphilitic and alterative. Hypodermic dose 1-5 to 1-3 grain.

Mercury Thymolacetate. (Mercuric) Indicated in syphilis, tuberculosis, etc., and injected intramuscularly, 1½ grains in liquid paraffin or glycerin every 3 to 5 days.

Mercury Thymolate (Mercuric). Indications and uses same as of the Thymolacetate, the latter being preferable.

Mercury Thymolnitrate. (Mercuric). Indications and uses same as of thymolacetate.

Mercury Thymolsalicylate. (Mercuric). Indications and applications same as of thymolacetate.

Mercury Tribromphenolacetate. (Mercuric).

Antisymphilitic, and used hypodermically in syphilitic joint diseases, in scrofula and tuberculosis. Merck gives the dose as follows: 8m of a mixture of 100 grains of mercury tribromphenolacetate, and liquid paraffin $4\frac{1}{2}$ drams once a week.

Mercury and Ammonium Bichloride. (Mercuric). Antisymphilitic and alterative. Hypodermic dose, 1-3 grain in 8m of water.

Mercury in oil, in various strengths is also employed hypodermically.

CHAPTER VIII.

Antitoxins and Serums.

In the discussion of biologic products, employed hypodermically in the treatment of diseases of an infectious nature, in view of the fact that there has been gathered together in the Mulford Working Bulletins, and that such matter is wholly of a scientific nature, we shall quote largely therefrom.

Diphtheria Antitoxin.—The mode of preparation will not be entered into at this time, as it is so well known as not to require comment. Suffice to say that since the introduction of this agent the mortality from diphtheria has become practically nil.

The technic of injection of antitoxins is similar to that of all other hypodermic operations. The serum may be administered either subcutaneously or intravenously. The latter method is preferable when prompt action is desired. Early in the history of diphtheria antitoxin the dosage was comparatively small, but today we see 10,000 or more units given initially, and in many instances such single large dose suffices. At an early date the serum was not concentrated and more or less trouble followed the

exhibition of large doses on that account. To-day, with the highly concentrated antitoxin, a large dose is possible without discomfort to the patient. The preferable site for subcutaneous injections is beneath the left scapula. The antitoxin should be employed at the earliest possible moment; in fact, injected upon suspicion. When this has been done it has been the experience that, with the infection present, the attack has been largely mitigated in fury because of such prompt action. Antitoxin, in dose of 1000 units, should invariably be injected in all persons who may have been in contact with the patient prior to, or who are to be his attendants, in that they may be immunized against the infection. It has been shown that such immunizing doses are very effective.

In mild cases, if treated early, the dosage ranges from 3000 to 5000 units, while in severe cases it ranges from 7,500 to 10,000. If a single dose shows no apparent improvement in from 6 to 8 hours, a second dose of like number of units should be given and a third repetition at like interval, if required. Age and condition of patient have but little to do with the dosage, in fact infants and feeble adults, being more prone to lack of immunity, require, and do well, on large dosage. The robust may not require as much of the antitoxin as do the feeble or young, because of their greater vitality and ability to combat the infection.

When employed as a prophylactic, too small doses should not be administered, not less

than 1000 units, as 500 will not afford entire immunity.

In the treatment of the established disease, it should invariably be remembered that half-hearted measures should never be resorted to, but that full dosage, and that only, as a rule, and at an early stage, will be effective. Also that the large initial dose not only acts in a curative manner, but overcomes the tendency to subsequent paralysis.

Tetanus Antitoxin.—Tetanus antitoxin is administered in the same manner as is the diphtheria serum. However, today we find the intravenous method gaining in popularity. This product is employed both for its prophylactic and curative effects. For the former action the serum is administered as soon as possible after suspected infection has occurred, and prior to the expiration of the period of incubation. It has been found that, when exhibited thus early, the antitoxin exerts an immunizing effect. Immediately, or as soon as possible after a wound, considered suspicious, has been received, the immunizing dose of 1500 units should be administered, and at the same time the wound itself should be freely incised and opened to the air, in that the tetanus germs may have a poor ground upon which to grow, they being, as is known, anaerobic. The wound should be treated antiseptically and tincture of iodine applied. If there is reason to believe that any of the tetanus organisms have been retained with-

in the wound as shown by continuous suppuration, a second like dose should be administered at the end of eight days. If the condition has passed into one of true tetanus, immunization is out of the question, and the curative dose of the antitoxin administered. As with the diphtheritic serum, the initial dose should be large, from 10,000 to 20,000 units and repeated at intervals of from four to six hours and continued until all symptoms of tetanus disappear. Tetanus antitoxin may be administered by injection within the spine, and it is said that good results have followed this method. The reports, however, are meagre at present. If the toxin has not united too thoroughly with the nerve tissues, prior to the use of the antitoxin, good results, it is said will follow. This complete union has had much to do with the failures reported, as the antitoxin is powerless to break up such union when once thoroughly perfected. However, the antitoxin is the only real specific we have in this condition, and it should invariably be employed, regardless of the fact that it sometimes fails. With the adoption of the large dose it may prove of still greater value.

Anti-Dysenteric Serum.—With the recognition that dysentery was due to bacterial origin, steps were taken to perfect a serum of an anti-dysenteric nature. Relative to this serum and its application we quote from an article on the subject by Dr. Frederick P. Gray, which ap-

peared in the University of Pennsylvania Medical Bulletin, November, 1902, as follows:

"There is no longer any doubt as to the existence of a form of dysentery which is specific in the full sense of the term. The particular bacillus isolated by Shiga (Central bl. f. Bakt. u. Parasit. 1898, xxiii, 599) in Japan, now demonstrated to be the cause of the disease, chiefly through the researches of Dr. Flexner (Phil. Med. Jour. 1900, vi, 414) and his pupils, has been shown to be the cause of acute and subacute dysentery of the tropics and institutional epidemic diseases in temperate climates. Confirmatory evidence relating to its etiological role has come from Germany and Holland (Kruse: Deut. med. Woch. 1900, xxvi, 637; 1901, xxvii, 370; Spronk (quoted by Kruse): Deut. Med. Woch. 1901, xxvii, 370), and Duval and Bassett (Am. Med. 1902, iv, 417) have recently established the causal relation between the bacillus and the summer diarrhea of infants.

"The importance of a pathogenic organism so widespread and with such varied capabilities as is exhibited by the bacillus of dysentery cannot well be overlooked. The prevalence of bacillary dysentery in the tropics and the marked susceptibility to the disease presented by a foreign population in those regions makes an attempt to check its progress, on the one hand through vaccination of those exposed to the infection and on the other through a specific therapy, a desideratum well worth accom-

plishing. And now that the destructive enterocolitis of summer origin in children can be ascribed to a similar form of infection, the procuring of a curative serum will constitute nothing less than a great boon to humanity."

Preparation of Anti-Dysenteric Serum.—In the preparation of the anti-dysenteric serum, horses are immunized by inoculation with the several strains of dysenteric bacilli—Shiga, Flexner, Kruse and Duval—and the sera produced are indicated by these names. The method of immunization is similar to that employed in the production of the diphtheritic and tetanic antitoxins. During the earlier days of production of anti-dysenteric serum, that drawn from horses immunized for four or five months was employed, but it was found to be relatively weak in curative action, and Kinyoun insisted that it required at least 11 months immunization of the horse prior to the time that a serum of therapeutic value could be obtained. Today the various sera employed are obtained from animals immunized for a period of much greater time, and such sera are found to be practically invariably active therapeutically.

Protective Power of Immune Serum Against Living Cultures of B. Dysenteriae.—Again quoting from the article by Gray, we obtain the following information:

"In the following experiments the serum used was taken with sterile precautions and inoculated into the guinea-pig without addition of a preservative. Inoculations into the loose

subcutaneous tissue of the back have been used unless otherwise stated.

"The protective power of the different immune sera were tested against multiple M. L. D. of living dysentery organisms. Repeated experiments prove that no protection against the dysentery organism is afforded by normal horse serum, and that perfect protection is afforded by previous subcutaneous injections of the serum of a horse immunized against the strain of B. dysenteriae used. Identical specific protection is shown by the sera of horses immunized with vaccines of the other three strains of B. dysenteriae, as shown by Tables I, II, III.

TABLE I.—Protective Power of Serum from Horse "Kruze" (Treated for Five Months) against Kruze Strain of B. Dysenteriae.

Weight of guinea pig.	Dose of serum 24 hours before	Strain of B. dysenteriae.	Intra-perit M. L. D.	Result.
270	Control	Kruze	5	Dead 18 hours
260	6 c.c.	"	5	Recovered
250	"	"	5	"
240	"	"	5	"
285	"	"	5	"
250	"	"	5	"

TABLE II.—Protective Power of Serum from Horse "Shiga" (Treated for Five Months) against Shiga Strain of B. Dysenteriae.

Weight of guinea pig.	Dose of serum 24 hours before	Strain of B. dysenteriae.	Intra-perit M. L. D.	Result.
265	Control	Shiga	3	Dead 18 hours
280	6 c.c.	"	5	Recovered
275	"	"	5	"
275	"	"	5	"
290	"	"	5	"
250	"	"	5	"
265	"	"	5	"
265	"	"	5	"

TABLE III.—Protective Power of Serum from Horse "Flexner" (Treated for Five Months) against Flexner Strain of *B. Dysenteriae*.

Weight of guinea pig.	Dose of serum 24 hours before	Strain of <i>B. dysenteriae</i> .	Intra-perit M. L. D.	Result.
290	Control	Flexner	5	Dead 20 hours
300	6 c.c.	"	5	Recovered
285	"	"	5	"
285	"	"	5	"
285	"	"	5	"
300	"	"	5	"
285	"	"	5	"

TABLE IV.—Amount of Flexner Serum Necessary to Protect against M. L. D. Intraperitoneally of Flexner Strain.

Weight of guinea pig.	Dose of serum 24 hours before	Strain of <i>B. dysenteriae</i> .	Intra-perit M. L. D.	Result.
250	Control	Flexner	7	Dead 20 hours
250	6 c.c.	"	7	Recovered
215	4 c.c.	"	7	"
250	2 c.c.	"	7	"
230	1 c.c.	"	7	"

"These subcutaneous doses of protective serum have been made intentionally large for the purpose of comparisons that are to follow; that the amounts used are far in excess of the quantity necessary to secure complete protection is shown by Table IV."

Protective Action of Immune Serum Against the Vaccines of *B. Dysenteriae*.—"In addition to their protective action against living cultures of the dysentery organisms, the immune sera are found to afford, as would be expected, distinct protection against the fatal toxic effects of dysentery vaccine.

"The protective power of the serum of the horse imperfectly immunized to the bacillus of

dysentery against such bacillary inoculation of the guinea-pig can be taken as proven beyond peradventure. The experiments in which this fact is established are equally conclusive as regards infection through living organisms and intoxication through dead ones. Such successful results in the guinea-pig, in which the pathological process is rapidly developed and quickly generalized in contradistinction to the slower evolution and localized character of bacillary dysentery in man, may be taken to augur well for the therapeutic application of the serum in the human disease. There is every reason for believing that a serum many times stronger and correspondingly more potent than that here described, will eventually be obtained. (Such a serum is now obtainable).

"At this writing (October 1, 1902) evidence of considerably greater progress in respect to the immunization, as compared with the state existing three months previously, is at hand. (Now, in 1913, there are furnished sera from horses immunized one, two and more years. Two strains of the *B. dysenteriae* are employed in such immunization, the Shiga (Japan) and the Flexner (Manila), in order that we may possess sera known to combat the different types of infection, non-acid and acid.)

"That the hope of successful application of such a serum therapy to man is not entirely speculative can be shown by a consideration of the published results by Shiga (Sei-I-Kwai, *Med., Jour, Tokyo*, 1901, **xx**, 89; *Deut. med.*

Woch. 1901, xxvii, 741, 765, 783) of the serum treatment of Japanese dysentery. While details are not yet available, Shiga states that of 250 cases treated with antidysenteric serum the mortality averaged 10 per cent. as against 36 per cent. in cases treated by ordinary methods."

In the remarks upon the subject made in American Medicine, Sept. 13, 1902, relative to work done in the laboratories of the Thomas Wilson Sanitarium and the Rockefeller Institute for Medical Research, we find the following:

"A careful study of the bacterial flora of a number of cases was made and from forty-two typical cases of summer diarrhea we succeeded in isolating from the stools the bacillus dysenteriae, Shiga. The specific organism was secured also from scrapings of the intestinal mucosa at autopsy, and in one case, from the mesenteric glands and liver. The dysenteric bacillus was present often in large numbers in the stools of acute cases, but was secured with difficulty from the cases of mild character and those of long duration on account of its presence in relatively small numbers and the antagonism of the normal intestinal bacteria. The specific bacilli isolated from different cases of the disease are identical, and agree in morphology, cultural features, pathogenic properties and reaction to specific serum with the dysenteric bacillus isolated from cases of acute dysentery in adults by Shiga in Japan, Flexner

and Strong in the Philippines, Kruse in Germany and lately by Vedder and Duval in this country. Agglutinative reactions when the organisms were tested, (a) with the blood-serum of the patients from whom they were secured, (b) with the serum of other infants suffering from summer diarrhea, (c) with the serum from adult patients with acute dysentery, (d) with anti-dysenteric immune serum. The specific bacillus was not found in the stools of twenty-five healthy children, nor those suffering with simple diarrhea, marasmus and malnutrition; nor did the blood-serum of these latter individuals agglutinate the dysenteric bacillus.

"We believe our findings justify us in the conclusion that the summer diarrheas of infants are caused by intestinal infection with the bacillus dysenteriae, Shiga, and therefore, are etiologically identical with the acute bacillary dysentery of adults. The cases studied, from which the dysentery bacillus was isolated, include examples of so-called dyspeptic diarrhea, or enterocolitis and of malnutrition and marasmus with superimposed infection.

In relation to the pathology of dysentery, and the preparation and results following the use of anti-dysenteric serum, the following is quoted:

"Shiga (San. Rep. U. S. Marine Hosp. Serv. 1897) in 1897 published the results of his investigations on the epidemic dysentery in

Japan. He found the cause to be a bacillus, which he designated the *Bacillus dysenteriae*.

"Flexner (Phil. Med. Jour. p. 414) and Strong (Rep. Surg-Gen. U. S. A., 1900) found what they determined to be the same organism in cases of acute epidemic dysentery occurring in the Philippine Islands.

"Kruse (Deut. med. Woch., 1901, p. 370), in an exhaustive investigation found an organism isolated with acute epidemic dysenteries occurring in certain institutions in Germany.

"Vedder and Duval (Jour. of Exp. Ped. 1901) also made a study of dysentery in the United States and found the same organism. It has been found also in Puerto Rico.

"The distribution of this organism appears to be quite general, and there can be but little doubt at the present time but that it is responsible for nearly if not all, the cases of acute dysentery of bacillary origin occurring in all parts of the world.

"In a summary of a discussion before the Pathological Society of New York (Arch. of Ped. Nov. 1903) Professor Simon Flexner stated that there are two well-defined groups of organisms isolated with dysentery in adults and children, the non-acid or Shiga group, and the acid, or Manila group. He believes that the future must determine what relation the non-acid or Shiga group, bears to the etiology of summer diarrhea in children. So far, his observations confirm the statements made by Vedder and Duval that the acid-producing

group predominates in the summer diarrheas. There seems to be a difference of opinion as to the importance which should be attached to the presence of the Shiga (dysentery) group of organisms in its relation to summer diarrhea.

"W. H. Park did not believe that the Shiga bacillus was present in the larger proportion of the summer diarrheas, as it has been his experience that this organism is not found, unless there are distinct symptoms of dysentery where the discharges contain mucous and are tinged with blood.

"Koplik regards the question as very complex, believing that the Shiga group is found in a limited number of cases. He reports that in the Babies' Hospital there were thirty-seven cases of summer diarrhea in which the dysentery bacillus was found. These cases were acute colitis, with bloody stools.

"Knox's investigation, conducted at the Wilson Sanitarium during the summer months of 1903, reports that there was nothing very striking in the character of the stools or pathological conditions found in the autopsy to differentiate the cases in which the dysentery bacillus, acid type, was found from the ordinary typical summer diarrhea. He is inclined to believe that a large group of both acute and chronic cases will be found to be due to this organism.

"Wellstein reports sixty-two cases of summer diarrhea in infants from two months to two years old occurring during the three summer months. Of these sixty-two cases, forty-seven

were found to be due to the Shiga bacillus. The mortality rate ranges from 55 to 78 per cent. according to the institution. In stools containing much mucous and blood the Shiga bacillus was more readily isolated than when the contrary obtains.

"Cordis reports fifty-two cases studied with reference to the presence or absence of dysentery bacillus. Of this number, twenty-six cases showed the organism, twenty-five were of the acid group and one of the non-acid group. The blood of forty-five of these cases was tested for its agglutinating effect upon the organism, and in only ten was there any agglutination to both the Harris and Shiga types of bacillus.

"Duval and Scorer report the results of their observations, conducted at the College of Physicians and Surgeons, of seventy-nine cases of summer complaint ranging from mild diarrhea to bloody iliocolitis with exudation. Examination was made of the stools almost immediately after passing, and upon this they ascribe the large amount of success in isolating the bacillus of dysentery. Of this number the dysentery bacillus was isolated in seventy-five cases, or 94 per cent. In fifty-eight cases of these the acid-producing type was found; in five cases, both the acid and non-acid producing type, and in twelve cases, the Shiga type. Four cases were negative.

"In 1902 forty-five cases of cholera infantum were examined by Duval and Bassett at the Thomas Wilson Sanitarium, Baltimore, and in

forty-two of these cases organisms were isolated which by their cultural characteristic reaction to the immune sera, were found to be identical with the *Bacillus dysenteriae*. In the beginning it was held by some that the organism which had been isolated from these several groups of cases in various parts of the world were one and the same. This opinion was based on the morphologic agglutinating reaction with the blood of cases recovering from dysentery of that of an animal immunized against the bacilli. Lentz (*Zeit. fur Hyg.* 1902) shows that there are two well defined groups of these organisms, one of the Shiga alkaline type and the other of Flexner, or acid type. During the summer of 1903 this subject was further investigated in this country with particular reference to its relation to summer diarrhea.

"Shiga claims that this organism does not as a rule invade the tissues other than those of the intestinal tract. It may sometimes, however, be found in the mesenteric glands. This organism in its growth in the intestinal tract secretes a virulent poison very much after the nature of the cholera spirillum. This has a dual action, one directly upon the intestinal coat and the other systemic. Recent investigations made by Shiga and Neisser show that this toxin of the dysentery bacillus can be isolated from cultures and when injected into susceptible animals like the rabbit or guinea pig produces symptoms of paralysis and profound changes in the intestinal mucous membrane of both the

small and large intestines. They believe that this poison, even when absorbed into the system from the intestine, is finally eliminated by the intestine.

"From the observations made in this country during the past two years, it is demonstrated beyond a doubt that cases of subacute bacillary dysentery occur throughout the whole year. This has been encountered in the dead of winter in the hospitals of Philadelphia and elsewhere. Epidemics of the disease seem to occur only when the conditions are ideal for its growth and development, and naturally the summer months offer the best conditions for development.

"The mortality of dysentery varies considerably according to the time and place. The usual mortality accompanying the disease in Japan has never been duplicated anywhere, save, perhaps, among the troops of the late Civil War. In this respect it is very difficult to ascertain from record, etc., the mortality of bacillary dysentery at this time because of it being so recently under investigation with reference to its cause. No reports, save those of Wellstein, have so far been published regarding the mortality of cases of summer diarrhea. It would not be wise to draw a hard-and-fast conclusion from these cases because so far as observation goes, the majority of cases of children received into the hospitals of cities during the summer months, are in what may be said the last stages of the disease. Many cases

of summer diarrhea occurring in the private practice of physicians are exceedingly mild. In fact, the epidemics may be mild, but at other times they may be severe. The same may be said with regard to the dysentery of adults. Some of these epidemics are mild, while others may be severe.

Pathological Anatomy.—"Howland examined thirty-two cases. In five cases there was a pseudo-membrane in the colon and ilium. The membrane was composed of necrotic tissue and disintegrated cells containing countless bacteria. Fibrin was present in small amount, if at all; there was necrosis of the mucosa. The necrosis did not extend beyond this coat. On the border of this necrotic tissue there were small hemorrhages with thrombosis. There was a line of sharp demarcation dividing the sound tissue by a zone of small round cell infiltration. Cells were of the mono and poly-nuclear type. A large number of "mast" cells were found around the small blood vessels. In another group (four cases) the mucous membrane was in good condition, the changes occurring almost wholly in the lymph follicles. The spleen, as a rule, was not affected. The kidneys showed cloudy swelling. Cultures made from all the organs were negative as to the *Shiga bacillus*."

Serum Therapy.—"Shiga reports that in 1119 cases treated in the hospitals at Tokyo, there was a mortality of 28.5 per cent. During the

same time there were treated with the serum in

1898 65 Cases.

1899 91 Cases.

1900 110 Cases.

266 Cases.

with a mortality of 9.6 per cent, as compared with those not treated 32.6 per cent. During the years of 1899 and 1900, 400 cases were treated. Those treated early and in the hospitals the mortality was 9 per cent., while those treated at their homes and in private practice the mortality was 12 per cent.

“Koplik reports that eight cases of cholera infantum were treated with anti-dysenteric serum. In three of these there was a striking improvement soon after administration of the serum, in others there was no improvement.

“Parke states that during the summer of 1903 some experience in these cases and their treatment by serum was secured by the New York Board of Health. About fifty cases were under observation, and one-half of these were treated with serum. Some of the mild cases did not seem to be much improved by this treatment, although none of them became worse. Bad cases treated with the serum apparently did better than corresponding cases without serum.

“During the summer of 1903 experiments were undertaken under the direction of Dr. Simon Flexner at Boston, New York and Baltimore with this serum. During the month of

May, 1904, an extensive use was made of anti-dysenteric serum in Southern countries and in the tropics, followed with most satisfactory results."

Dosage.—"The same rule holds in the administration of anti-dysenteric serum as with the anti infections serums and antitoxins, the necessity of early administration of the serum in all cases, and where employed late in the disease, large doses must be administered.

"As a rule, in cases treated early 10 c.c. to 20 c.c. of the serum should be administered every six to twelve hours; in cases treated late, or of unusually severe type, 20 c.c.

Antipneumococcic Serum.

Anti-Pneumonic Serum.—See Pneumo-Bacterin.

Anti-Streptococcic Serum.—See Strepto-Bacterin.

Antimeningitis Serum.—Antimeningitis serum is prepared, as are other serums and antitoxins through immunizing horses with steadily increasing doses of first killed, then living meningococci, until at the end of six months, if a dilution of 1 to 5000 of the serum of the animal shows bacteriotropic power, it is of sufficient strength for therapeutic use. If such power is not exerted, the inoculations are continued until this is attained.

Dopter (Annales de L'Institut Pasteur, Vol. xxiv, 1910, p. 96) says that antimeningitis serum prepared by subcutaneous inoculation of

horses with meningococci and autolyzed cultures, possesses the following properties:

"1. It contains agglutinins specific for the meningococcus and also 'co-agglutinins' for the pseudo-meningococci (gonococci, etc.) as is shown by the saturation of these organisms by the agglutinins.

"2. It contains precipitins, which are shown when one mixes the serum, even in very high dilutions, with the extract of meningococci. The mixture, left at room temperature, first becomes cloudy and then gives rise to a precipitate which collects at the bottom of the test tube. The same precipitate may be produced with extracts of pseudo-meningococci (*diplococcus crassus*, *gonococcus*, etc.). The test of saturation of complement shows that the precipitation in this case is a co-precipitation or 'precipitation in group.' If the serum is heated several times at 55° it loses in large part its power to produce precipitins.

"3. It contains specific amboceptors, the existence of which show by the test of deviation of complement. Deviation of complement may be produced equally well with a microbic emulsion, or with the autolyzed culture. It can be effected only by the meningococcus; even the most closely related organisms give negative results."

Neufeld and Kraus say that the serum possesses bacteriotropic powers and that the determination of this is the basis upon which to determine the therapeutic power. It does not, on

the other hand, possess bactericidal power. They determined the antitoxic powers by injecting, intraperitoneally, young guinea pigs with a mixture of the serum and autolyzed cultures, and found that, as a rule, 1 c.c. of serum would neutralize five fatal doses of the meningococcic endotoxins.

Not only is the serum of those horses immunized in the usual way of therapeutic value, but likewise is that of horses immunized by the intravenous injections of living cultures.

That antimeningitis serum is of great value in the treatment of cerebro-spinal meningitis is shown by the facts that it very markedly diminishes the mortality; that it influences the symptoms in practically every case in which it is used; that it reduces the duration of the disease, and practically overcomes any tendency to sequelae.

Under the older lines of treatment, it is shown by statistics that the mortality in epidemics has ranged from 30 to 80 per cent., with 100 per cent in young infants. In one series of cases, reported by Flexner, in which the serum was employed, the mortality was only 25 per cent. On the continent it is reported by some that the mortality has been reduced still farther, to 18.35 per cent. From 53 per cent., Schone reports a reduction to 27 per cent., and Jehle one from 80 to 45 per cent. In the epidemic of 1909, in France, Dopter reported a total of 402 cases, with 66 deaths, or a mortality of 16.44 per cent. Of the cases reported 19 of

those who died were in extremis when first inoculated with the serum, or death was due to other than directly to meningitis. Deducting these cases, the mortality was 12.27 per cent. in all other cases treated. Those cases treated without serum in the same epidemic showed a mortality of 65 per cent. All reports point to the fact that the early use of serum is followed by greater successes than are the latter ones.

As a rule, after the intraspinal injection of the serum, and within twenty-four to forty-eight hours, there is a remarkable reduction of all symptoms. The temperature falls, and in some cases may fall to normal, with prompt defervescence, or the fall may be by lysis, and there is relief from headache, coma, insomnia and delirium and although stiffness of the neck usually persists to some extent, longer than do the other symptoms, it likewise shows early relief. In some instances there is slight rise in temperature after the injection, but this is, as a rule, followed by a prompt fall. With the other symptoms, the auditory and ocular phenomena disappear and the paralysis is overcome. The patient generally shows improvement, with disappearance of the facial pallor, the typhoid condition and signs of toxemia. The serum produces a marked effect upon the spinal fluid, the degenerated polynuclear cells are lessened and replaced by normal cells of that character, with a lessened number of meningococci, which finally completely disappear. Those remaining show disintegration. Finally

cultures from the spinal fluid are sterile. The meningococci are absent and the polynuclear cells become less abundant and become gradually replaced by mononuclear cells, with the establishment of convalescence and recovery. That the spinal fluid returns to normal is likewise determined by chemical test, showing the lessening of albumin, glucose, etc., contents of the fluid and by the disappearance of products of bacterial disintegration. This latter is shown by occurrence of the precipitin reaction. That the serum is beneficial is shown by the fact that in some cases, improvement takes place while the injections are being given, but that the symptoms reappear with the withdrawal of the serum, to again disappear when inoculations are resumed. In other cases, all the symptoms do not show coincident improvement; the temperature may fall, but the nervous symptoms remain; the general condition may show no marked change, may be even precarious, while those of a meningeal character may entirely disappear, and these suggest that some modifications should be made in the treatment.

Those cases which show but little improvement, or none at all, are those in which the condition is of the fulminant sort; those in which injection has been made late in the course of the disease; where the disease assumes the septic type, as shown by hemorrhages and large petechiae and extra-meningeal complication, as broncho-pneumonia or nephritis; those of a cerebral type, with the disease limited to the cran-

ial regions, and which are reached with difficulty with the serum by intraspinal injection; in those cases where, although the serum produces improvement initially, the disease, after a time passes into the chronic stage and in those cases where the serum has no effect upon the meningococci in the cerebro-spinal fluid. Why this is so, is not clear. It is explained that it may be due to the fact that the lesions are located on the vertex or in the cerebral ventricles, and are not accessible to the action of the serum through direct contact.

Prior to the use of the serum it was a common thing to see cases lasting two, three and four weeks, whereas the average duration, since the introduction of inoculation has reduced the duration to from eight to twelve days, and with a return to the normal condition and without sequelae, as was the case under the older treatment. The reduction of duration has much to do with the lack of occurrence of sequelae. Instead of a percentage of 23 sequelae, as reported by Netter, Dopter reports only 2.56 per cent. Under the treatment without serum deafness, blindness and paralysis were present following the disease in from 70 to 80 per cent. Netter, following the use of the serum, reports only 7.5 per cent. of sequelae, and in 402 cases only 6.2 per cent., and most of them lesions of the internal ear. No complications have been noticed which were not present prior to the first injection of the serum.

The serum, introduced into the spinal canal

acts directly upon the meningeal lesion, and at a distance upon the general organisms. Locally it brings about modifications of the cerebro-spinal fluid, as is shown by disappearance of pus corpuscles, the presence of unlabeled polynuclear cells and by the disintegration and final disappearance of the meningococci. The latter is believed to be due to bacteriolytic power upon the part of the serum, and it is likewise believed that the serum neutralizes the endotoxin set at liberty in the fluid. Owing to the presence of intact polynuclear leucocytes, many believe that the serum acts by stimulation of phagocytosis. That bacteriolysis occurs, is explained by the occurrence of intracellular digestion of the bodies of the leucocytes. The liberated endotoxin may be absorbed and destroyed by the same cells.

The serum permeates the general organism through absorption from the membrane of the cord into the general circulation. According to Netter, in one case of meningococcemia, in which meningitis was not present, intraspinal injections of the serum were followed by satisfactory results. That other symptoms than those of the brain or cord, such as petechial eruptions, albuminuria, and others, disappear with the injection of the serum, are indicative of general absorption.

That injections of diphtheria antitoxin and other sera have no effect in cerebro-spinal meningitis, and that antimeningitis serum has a

marked one in a curative way, is indicative that the latter is a specific in this disease.

Method of Employment.—Quoting from Working Bulletin No. 8, we obtain the following data relative to the technic of application of antimeningitis serum:

It has been shown that as the diffusion of fluids into the spinal canal is quite slow, the best results are obtained if the serum is injected directly into this canal. In a few cases in which the symptoms were entirely cerebral and in which intraspinal injections produced little or no benefit, the attempt has been made to inject the serum through the open fontanel of young infants directly into the ventricles of the brain. But these experiments have been too few in number for any opinion to be expressed as to the efficacy of the procedure. It is perhaps worth trying in such cases as have been mentioned.

All authors insist upon the necessity of using large doses, even in young infants. In the adult one may inject 20, 30, 40 and even 45 c. c. of serum, provided a similar amount has been withdrawn by lumbar puncture. In infants less than one year old, one may easily inject 10 to 30 c.c.

Except in mild attacks, one injection is rarely sufficient to effect a complete cure. After the first injection all the symptoms may improve so that one considers a second injection unnecessary and believes the patient is cured, but the next day, or the day after, there may be

a recurrence of fever and meningeal symptoms, and a fresh injection is necessary. This may be explained by the fact that the serum introduced into the spinal canal has been absorbed from this before its effect has been fully developed. Some authors give one injection, and if there is no improvement they repeat it until improvement is secured. If the symptoms continue to improve they give no further injections. Other authors consider that it is better to inject systematically 20 to 30 c.c. of serum daily for three or four consecutive days, even when the first injection has produced marked improvement of the temperature and of the symptoms. According to Netter, the repetition of injections presents the greatest advantage of producing more cures and the shortening of convalescence, as well as lessening the tendency to recurrence and sequelae. A fall of temperature is not sufficient reason to believe that the dose of serum has been sufficient, as in a certain number of cases the other symptoms do not improve coincidentally, and in some severe cases there is little fever. For this reason it is better to base the use of the serum on the other symptoms. The most valuable sign is the appearance of the cerebro-spinal fluid. If after the injection meningococci which have undergone degeneration are discovered, it is necessary to continue the injections. If after several daily injections the fluid contains no meningococci and the degenerated leucocytes have been replaced by normal, no further injections are necessary, even

though the temperature does not fall. It is wise, however, to draw specimens of fluid for examinations, at intervals of several days, and if the meningococci are found, to inject the serum. In cases of sequelae, or recurrence, if there is doubt as to the advisability of the use of the serum, the question is best decided by bacteriologic study of the cerebro-spinal fluid. If meningococci are present, the use of the serum is indicated; otherwise not.

If the cases treated by serum are divided into two groups, those in which only one dose or insufficiently large doses are given, and those in which sufficiently large and frequently repeated injections were used, we find the following results: In the first group, 77 cases with 21 deaths; namely 27 per cent. In the second group, 282 cases, with 23 deaths, namely 8.15 per cent. A comparison of these figures shows that it is not sufficient merely to inject the serum. It must be injected in sufficient quantity, and repeatedly, in order to obtain the best results from its use.

Dunn (Boston Md. & Surg. Jour. 1908, clxx, p. 743) emphasizes the necessity of injecting the antimeningitis serum into the subdural space and of using sufficient doses. His present practice is to regard 30 c.c. as a minimal dose, except in very young infants and in cases in which only a small amount of fluid can be withdrawn and an obstacle is encountered before the entire quantity of serum has been injected.

As a rule, the serum passes readily into the spinal canal, when injected either by means of a syringe or by means of gravity, using a funnel connected with the needle by a rubber tube. In all cases it is essential to remove as much cerebro-spinal fluid as possible, as it is desirable to make space for the serum. Free aspiration presents the advantage of making a form of negative pressure in the ventricles which draws the serum upwards toward the brain. The spreading of the serum into the skull may also be favored by placing the patient with the head a little low, immediately after completing the injection. If more than 30 c.c. of fluid is withdrawn, the amount of serum injected may be correspondingly increased. In severe and fulminant cases the full dose of 45 c.c. should be introduced, unless indications exist to the contrary.

The effect of a single injection tends to pass off in rather more than twenty-four hours, after which time the symptoms return. It is best however, not to wait for the return of the symptoms. The injection should be repeated at intervals of twelve to twenty-four hours until four injections have been given, even though the diplococci disappear from the spinal fluid and the symptoms clear up. If the organisms have not entirely disappeared from the fluid at the end of four days, the injections should be continued until no more organisms are found. In severe and fulminant cases the second injection should be given at the end of twelve hours,

and if there is no improvement a third injection should be given at the same interval. The treatment of relapses is the same as the treatment of prolonged cases showing exacerbations of symptoms. Lumbar puncture should be performed immediately, and daily injections of full doses of the serum should be given as long as a diplococci can be found in the spinal fluid. At least four injections should be given at twenty-four hour intervals.

Finley and White (Montreal Med. Jour., Sept. 1908) state that the serum used in the treatment of cerebro-spinal meningitis should be injected slowly at the rate of 2 c.c. per thirty seconds. It is advisable to use a general anesthetic during the injection. If there is shock following the operation, camphor and strychnine may be injected hypodermically. The temperature usually falls after the first two or three doses of serum. All of the cases which came under treatment before the fifth day of the disease recovered. The only death was in a case which came under treatment later. If mild symptoms, such as a slight elevation of temperature, retraction of the head, or Kernig's sign persist after the bacteria have disappeared from the spinal fluid, a simple puncture may sometimes relieve these without the injection of serum.

The gravity method (J. A. M. A. Mar. 23, 1912, p. 843) of administration is strongly advocated by some clinicians, who claim that this method has many advantages and but few dis-

advantages of the syringe method. The after effects are usually less severe, the temperature lower, the patient feels more comfortable, the general condition better when the gravity method is employed.

The serum, after being warmed to body temperature (care must be exercised not to warm the serum beyond 100° F. otherwise it will coagulate) is introduced very slowly. An assistant takes the blood pressure readings throughout the operations. These readings indicate not only the quantity of serum that may be safely injected, but also the rate of injection.

The serum is allowed to run in very slowly by gravity, the flow being regulated by raising or lowering the syringe containing the serum, which admirably serves the purpose of a funnel. The barrel of the syringe being sterile insures a sterile funnel and prevents the danger of infecting the serum. The time taken for the injection is generally 10 minutes, though 20 or more minutes may be taken, especially in cases beginning with low blood-pressure, or when the blood-pressure drops very quickly. The blood pressure lessens continuously from the beginning of the injection.

The barrel of the syringe containing the serum is attached to 10 or 12 inches of rubber tubing about $\frac{1}{4}$ inch in diameter. With the average blood-pressure of 110 or 120 mm. of mercury, a total drop of 20 mm. in an adult is a safe indication to stop the injection. After a fall of 20 to 30 mm. it becomes relatively

much greater if injection is continued (e. g., 40 mm. more making a total of 60 mm. or more). An instance is mentioned in which this occurred—a few minutes later the patient's heart and breathing stopped, though response to immediate active treatment was prompt. Occasionally an initial rise is followed by fall as the injection is continued. Very rarely a material rise occurs after injection.

The treatment of severe symptoms consists in cessation of the injection upon a considerable fall; removal of fluid from the canal at once upon a sudden marked fall, by simply lowering the syringe-funnel; in grave cases artificial respiration; as adjuvants, epinephrin intramuscularly in large doses, other vascular stimulants and atropin. Immediate active treatment generally provokes response.

The average dose by the gravity method is 20 to 25 c.c. in adults; in children in proportion. Infants that cannot tolerate more than 2 to 4 c.c. respond remarkably well. When the blood pressure allows, from 30 to 40 c.c. may be injected, rarely more.

Clinical Reports.—In the original Working Bulletin No. 8, and the revised edition thereof of September, 1912, are the following clinical reports which are quoted:

Flexner (J. A. M. A., 1909, ii, p. 560) reports the results which had been obtained up to November, 1909, in the serum treatment of cerebro-spinal meningitis. He states that the reports have come from the pandemic of 1904-08.

The results obtained in the United States are not so conclusive as those obtained in Europe, because in this country the epidemic had already passed its height when serum treatment was first used, whereas in Europe it was still raging with full virulence. In Germany the epidemic was virtually at an end when serum treatment was instituted. In France, on the other hand, the serum was available at the beginning of the outbreak. The Rockefeller Institute sent supplies to Professors Calmette, Netter and Roux. The reports of the serum treatment now appearing in the French medical Journals are based chiefly on the use of the serum prepared at the Rockefeller Institute.

In France the mortality of cases treated with serum has been less than 25 per cent., while in cases treated without the serum it has averaged 80 per cent. The results obtained in this country and in England were quite similar. We have statistics of 712 cases in which a bacteriologic diagnosis was made. In these cases the total mortality was 31.4 per cent. In infants less than two years old the mortality was 42.3 per cent. In previous epidemics it has generally averaged upwards of 90 per cent. In cases where the injections were given within the first three days of the disease the mortality of infants less than two years old was only 5.8 per cent. There was no such striking difference between the results obtained by earlier injections in older persons. The total mortality of the cases injected before the seventh day was

26 per cent., and among those who received their first injection after the seventh day of the disease, it was 42 per cent.

During an epidemic the existence of the disease will often be suspected before meningeal symptoms are apparent. In such cases the diagnosis may be made by examination of the spinal fluid, which will usually be turbid and will always show the presence of meningococci. If the serum is injected immediately, such cases are almost always terminated or run a mild course.

Flexner (J. A. M. A., Vol. i, No. 25), in a paper read before the American Medical Association, states that more than 1000 cases of epidemic meningitis, diagnosed bacteriologically, have been treated with his serum. The serum is obtained by immunizing horses, first by means of dead and then by means of living cultures of meningococci, first injected subcutaneously and then into the veins. Of these cases 550 have been carefully analyzed and it is found that in Scotland and Ireland the mortality had apparently been reduced from 75 per cent. to less than 30 per cent. In Edinburgh the mortality had been reduced to about 40 per cent., and in Belfast to less than 30 per cent. In this country and France the results were much the same.

Abbott, in discussing this paper, said that his experience in Philadelphia had been very favorable. Twenty patients were treated with

the serum and the results were better than any other treatment ever tried.

Koplik stated that the results had been especially gratifying in children under two years of age. Up to that time he had treated six babies, from five months to two years old, with three complete recoveries.

Ewing remarked that a series of cases should be treated with injections of normal horse serum and the results compared with results from meningitis serum.

Dr. Flexner replied that he did not think it would be justifiable to carry out such an experiment on human beings, but that such a comparison had been made with monkeys, and the results obtained by the use of the meningococci serum were much better than those obtained by injections of normal horse serum.

In the Archives of Pediatrics, 1908, page 747, Flexner and Jobling report 393 cases of epidemic meningitis treated with serum. The cases have arisen in different and widely separated parts of the United States, Canada and Great Britain. Bacteriologic diagnosis was made in every case. Cases in which death occurred within twenty-four hours of the time of injection have been excluded from the summary, as it has been shown that the beneficial effects of the serum are not exerted until after this period. Of these 393 cases 295, or 75 per cent, recovered. The mortality of cases in which the first injection was given from the first to the third day of the disease was 16 per

cent; from the fourth to the seventh day, 24 per cent and later than the seventh day, 35 per cent. About 75 per cent of the cases treated with serum terminated by crisis. Relapses have not been frequent and fatal termination has been exceptional when the serum treatment has been resumed. The only sequel which was reported was deafness, which was seen in only a few cases.

Churchill (Arch. of Ped., p. 754) reports nine cases of meningitis in which the meningococcus was found, which were treated with the Flexner serum. Seven of these cases recovered, all without serious sequelae. The first effect noted clinically was the change in the patients' mentality. They seemed brighter and more rational after the first, second and third doses of the serum, as the case might be and this improvement continued steadily until the patient was well. It was a curious sight to see a patient with the head markedly retracted, yet perfectly quiet and without pain, interested in his surroundings. The temperature fell almost at the same time that the mental improvement began, and the leucocytosis diminished. Examination of the first specimen of spinal fluid obtained by spinal puncture generally showed large numbers of leucocytes and also meningococci, varying in numbers with the intensity of the disease. Subcutaneous punctures showed a fluid less cloudy, and containing fewer cells and organisms. Churchill believes that in a case of suspected meningitis it is our duty to do a lumbar

puncture, and if we obtain a cloudy fluid to inject at once into the spinal canal, subsequent injections being determined by the results of the bacteriological examinations of the spinal fluid. If this shows the presence of meningococci the serum should be repeated every day for three or four days, as necessary.

Dunn (Arch. of Ped. p. 756) reports 40 cases of cerebro-spinal meningitis treated with the Flexner serum. All the cases in which the diplococcus intracellularis was found are included in the series. The serum was administered into the spinal canal, as recommended by Dr. Flexner. If the fluid obtained by puncture was clear no serum was given unless the bacteriologic examination showed the presence of the diplococcus. But if the fluid was cloudy the serum was injected at once. The routine dose was 30 c.c., the maximum dose 45 c.c. If the amount of fluid obtained by puncture was small and increase of intradural pressure was feared, amounts as small as 10 c.c. were often injected. Thirty-one of the 40 cases recovered, one being deaf and one deaf and blind. The lowest mortality in any previous year was 58 per cent, varying between this and 80 per cent. The mortality in the year referred to by Dunn was only 19 per cent. under the use of the Flexner serum. Of the nine fatal cases in the series, five were seen quite late in the course of the disease, and in one case the serum was not given until the patient was actually moribund. Of the other four fatal cases one was of the

fulminating type, one very severe, and one died of intercurrent broncho-pneumonia which came on after the temperature had returned to normal and the meningeal symptoms had subsided. The fourth case was one of normal severity, in which the serum appeared to produce the improvement in the beginning, but which was later uninfluenced by the treatment. The most noticeable effect of the treatment is not its influence on the mortality, but the remarkable improvement which takes place in individual cases after the injection of serum. It produces first a fall in temperature; second, a rapid improvement in the patient's general condition, and, third, a shortening of the course of the disease. The first injection of serum is often followed by a critical fall, which is sometimes permanent. In other cases the temperature returns to a high point and falls by lysis. The effect on the general condition of the patient is most striking. There is a permanent return to consciousness and disappearance of delirium and headache as well as hyperesthesia and vomiting. These symptoms are often completely relieved within twenty-four hours after the first injection, the patient changing in the most remarkable way from a condition of coma to a condition of normal mentality and activity. The average length of time patients remained under treatment was but a small fraction of the time patients who recovered remained under treatment in previous years. Another marked effect of the serum

is as regards the character of the spinal fluid. The fluid first withdrawn is turbid and shows large numbers of leucocytes and diplococci. Twenty-four hours after the first injection the number of organisms is much smaller and the majority are intracellular, only rare extracellular forms being seen. The third lumbar puncture shows still fewer diplococci, and only intracellular forms. After the third injection it is unusual to find any diplococci. Relapses sometimes occur under the use of the serum, but these usually yield to repeated doses.

Although the serum is ordinarily without benefit in chronic cases, it may occasionally do good. One patient in the late chronic stage began to improve immediately after the first injection and made a rapid convalescence. There is always some hope of a good result as long as diplococci are present. The serum causes a cessation of the active process in most cases and the result of the disease depends mainly on the extent of tissue damage which has already been done. The value of this serum is comparable to that of diphtheria antitoxin.

Knox and Sladen (Arch. of Ped. p. 761) report 21 cases treated with Flexner serum in Johns Hopkins Hospital; three of these cases died, a mortality of 14 per cent. The effect of the first injection was usually a rapid fall in temperature. In one case this remained normal, but ordinarily there was a rise the next day and at least three injections were required

to induce permanent low temperature. From three to twelve hours after the injection the headache, delirium, and pain in the back began to disappear. Stiffness of the neck and Kernig's sign were more persistent. Pressure symptoms were often relieved by the treatment, although fluid obtained by puncture was always replaced by at least an equal quantity of serum. The effect on the spinal fluid was the same as reported by other authors. It seems probable that the serum has both an antitoxic and bactericidal power.

In discussing the above papers Dr. Koplik stated that he had treated 13 cases with serum, there being two deaths, both infants less than one year old.

In the discussion Dr. Wilkinson stated that he had treated 10 cases at the Garfield Hospital in Washington, with seven recoveries. Of the three that died, one had marked hydrocephalus, and one might possibly have been cured if larger doses had been given. The third case was in a comatose condition when the treatment was begun. There was considerable improvement in the meningeal symptoms and in the spinal fluid after the injection of the serum, but intestinal paralysis developed and the case ended fatally. The best results have been obtained with injections of from 15 to 30 c.c. The symptoms generally subsided in four or five days, the organisms at the same time disappearing from the spinal fluid.

In closing the discussion Dr. Flexner reported statistics from Belfast. During the height of the epidemic, a mortality of 75 per cent. was reported, although in the hospitals where the serum treatment was being used the mortality was only 26 per cent. The serum belongs to the class of bacteriolytic sera, in the preparation of which we are obliged to use the entire constituents of the organisms. We have three antitoxic bacteriolytic sera, diphtheria, tetanus and dysentery. The peculiarity of these sera is that any dose of the corresponding toxin may be neutralized if a sufficient amount of the serum is given. The antimeningitis serum, on the other hand, does not produce neutralization of the toxin according to the law of multiples. The dose of toxin can be made so great that the serum becomes ineffective. The important point in the administration of the serum is that it shall be given in sufficient concentration and directly into the spinal canal. If given into the circulation the secretion into the subdural space is slow and imperfect.

Chase and Hunt (Arch. of Int. Med. 1908, iii, p. 294) report an epidemic of cerebrospinal meningitis in Akron, Ohio, in which the Flexner serum was used. Twenty-two cases were seen. In 12 of these the serum treatment was used, with three deaths, a mortality of 25 per cent. In 10 cases the serum was not used, and nine of the patients died, a mortality of 90 per cent. The diagnosis was made in each case

by the finding of the diplococcus of Weichselbaum. The only medication any of the patients received aside from the injections of serum was an occasional hypodermic injection of morphine combined with hyoscine, when delirium and restlessness were pronounced. The 12 cases treated with serum are reported in detail. The authors ascribe the low mortality of the series to the use of the serum, as there was no other difference between these cases and the 10 cases previously mentioned.

Koplik (Med. Rec. 1908, ii, p. 557) reports 13 cases treated with serum. The punctures were carried out in the median line and the serum introduced, not with a syringe but with a funnel. A glass funnel holding about 20 c.c. is the best. The pressure exerted by the syringe is likely to be dangerous. Two patients were less than six months old, and in each case the disease had been in existence for several weeks. Both died. The 11 other cases recovered. The previous mortality had never been less than 40 per cent.

Ladd (Med. Rec. 1909, i, p. 1,055), in a paper read before the American Medical Association, states that the serum treatment was used in an epidemic of cerebrospinal meningitis in Ohio, in which the mortality had previously been 80 per cent. The serum was used in 31 cases, with 20 recoveries; a mortality of 35.5 per cent. All of the cases treated on the first day of the disease recovered.

Rotch (J. A. M. A. 1909, Oct. 30, p. 1,443)

of Boston stated that from November 1, 1907, to November 1, 1908, antimeningococcus serum was employed at the Children's Hospital, Boston, with the result that the mortality from cerebrospinal meningitis immediately fell from 80 per cent. to 19 per cent., and that it never went over 25 per cent., while before the employment of the serum the mortality had been from 60 to 80 per cent.

In addition to improved statistics of mortality, the conditions of the patients surviving were wonderfully improved. The terrible sequels—hydrocephalus, mental and physical deteriorations, blindness, deafness, paralysis—rarely ensue in cases treated with serum. Then, too, the duration of the disease has been markedly shortened, the old persistence for weeks and months being infrequent under the new treatment.

Past Asst. Surgeon R. H. von Ezdorf found, in the recent epidemic in Texas (1911-1912) that of 410 healthy persons who had been exposed to the disease, 59.6 per cent. were carriers of the meningococcus, and, from cultures, 53.75 positive carriers.

Dr. A. W. Nash, of the City Hospital of Dallas, Texas, states that experience gained in the recent epidemic of cerebrospinal meningitis in Texas has demonstrated that better results may be obtained by withdrawing from the cord not all of the spinal liquid that can be removed, but only that sufficient to relieve the pressure; furthermore, instead of in-

jecting sufficient antimeningitis serum to replace the amount of liquid removed, better results are secured when one-half as much serum is used as liquid withdrawn. That is to say, if 30 c.c. of spinal liquid are withdrawn, from 15 to 20 c.c. should be employed.

Up to January 27, 1912, reports of the State Health Officer listed a total of 550 cases and 210 deaths occurring in 49 counties of the state. In Oklahoma, in this epidemic as reported from December 1, 1911, to January 25, 1912, there were 72 developed cases and 2 suspects, with a total of 36 deaths in 14 counties. The spinal fluid was microscopically examined. Antimeningitis serum was used with the result that the mortality was reduced to 10 per cent. Without the serum the mortality was from 75 to 90 per cent.

Dopter (*Ann. de l'Inst. Pasteur*, xxvi, 1910, p. 96) reports that of 402 patients treated with the serum, 66 died—a mortality of 16.44 per cent. The author believes there is a danger in doses given in excess of 50 c.c. during 24 hours or if more than three injections are made in 24 hours.

Langfeld (*West. Med. Rev.* Apr. 1912, p. 201) reports 5 cases of cerebrospinal meningitis in which antimeningitis serum was used, with 5 recoveries; 4 patients were treated in a hospital and 1 at home. He withdrew as high as 60 c.c. of cerebrospinal fluid from one adult, replacing this by 60 c.c. of serum. During the first 24 hours 2 injections were given in all

except the mildest cases. Langfeld believes it is best always to give an anesthetic, and daily injections after the second until the specific diplococcus is no longer demonstrable by microscopic examination of the cerebrospinal fluid. Lumbar puncture is a harmless procedure, not difficult to perform, and should the cerebrospinal fluid withdrawn not be as clear as water, 30 to 45 c.c. of antimeningitis serum should be introduced, as no harm will result than from the subcutaneous injection of diphtheria antitoxin.

In the first case, a female patient, aged 22, the effect of the first injection was magical; from 2 to 4 hours afterwards the patient regained consciousness and called to the nurse for water and then for milk. In all, 220 c.c. were withdrawn and 225 c.c. of antimeningitis serum administered. In the third (a male of 14), 280 c.c. were withdrawn and 295 c.c. administered. In the fourth (female, age 4), 256 and 275, and in the fifth (female, age 11) 210 and 225.

Langfeld concludes:

1. While admitting the existence of fulminating cases, a large proportion have prodromal symptoms from 2 to 6 days before acute symptoms, during which state a positive diagnosis is possible by means of spinal puncture and microscopic examination of the cerebrospinal fluid.

2. That there is no danger in lumbar puncture.

3. That the antimeningitis serum is a specific for that form of cerebrospinal fever due to the *diplococcus intracellularis meningitidis*. Its action is immediate, bringing about:

(a) Rapid restoration to consciousness from delirium and mania.

(b) Equally rapid reduction in temperature, especially if this is very high.

(c) Miraculous disappearance of pain in the head and back; no other drugs required.

(d) Cessation of vomiting.

(e) Direct action on cerebrospinal fluid, which is quickly made to resume normal condition.

(f) Only by its use is there prevention of such sequels as deafness, blindness, etc.

4. That in injecting the serum the quantity introduced may be made greater than that withdrawn, if care is taken not to use too great force in its introduction.

Herold (J. A. M. A. Aug. 10, 1912, pp. 444-445) reports an extremely grave case of epidemic cerebrospinal meningitis in which the injection of 420 c.c. of serum brought about recovery. The patient, a school boy of 17, showed undoubted evidences of epidemic cerebrospinal meningitis, including rigidity of the neck, Kernig's sign and partial delirium. The case was an extremely grave one and twice the patient was considered "in extremis," when oxygen was administered. Thirty c.c. doses of serum were administered each day from the 1st to the 7th, except the 4th, when the patient

was thought to be in extremis. On the 8th day 60 c.c. were administered, followed in the next 30 hours by 180 c.c. in 3 doses, or 420 c.c. in all. One month after the onset of the disease the patient was discharged as cured. Herold believes that complete recovery would not have occurred had he stopped on the 8th day with 240 c.c.

CAUSES OF FAILURE.

In a certain percentage of cases the serum has seemingly failed without apparent reason. In discussing this question, the Journal of the American Medical Association, 1911, ii, p. 823, suggests the possible reasons for such failures:

"It is possible that the cause of failure to obtain good results from the use of antimenigitis serum sometimes experienced may be due either to an obstruction to the passage of the fluid, by a plug or pus, etc., so that the serum cannot reach certain parts of the brain infected, or to the fact that there are present strains of the diplococcus intracellularis other than the one employed in the preparation of the serum. For this reason preference should be given to a polyvalent serum, i.e., one obtained from horses immunized with many strains of the diplococcus intracellularis."

As has been cited by some authors, it is possible that some failures are due to the fact that the focus of infection is so located as not to be reached by injections within the spinal canal. Such instances have been mentioned in preceding pages.

AUXILIARY TREATMENT.

While the serum is a specific remedy, there are frequently indications for other therapeutic agents, and discussing the therapeutics of cerebrospinal meningitis, the Journal of the American Medical Association, 1911, ii, p. 823, gives the outlines of the auxiliary medical treatment as follows:

Nose, throat and eyes, too, if there is conjunctivitis, must be kept clean with antiseptics—for the throat a spray or gargle such as warm hydrogen peroxide solution (1:5); for the nose, a warm weak alkaline solution, e.g., diluted liquor antisepticus alkalinus; for the eyes, boric acid solution. The position of the body and limbs should be that which gives least pain and most comfort; painful joints should be wrapped with cotton.

Calomel, followed by a gentle saline, should be given. The patient should receive plenty of water, but food is best withheld for a day or two, especially if vomiting and anorexia are present. After that the simplest foods in small amounts, of which the best are milk, oat-meal gruel, egg-albumin, and, later on, meat-juice at three hour intervals, are advised. Persistent vomiting and intense nausea require hypodermics of morphine, the dose and frequency varying with the intensity and age of the child. To ensure sleep, muscle-relaxation and nerve rest-essential in the treatment of meningitis—chloral or bromides are indicated.

For relief of inflammation, ergot intramuscularly into the deltoid, or calves of the legs if it is repeated frequently. This drug is contraindicated only in excessive heart-action and high blood-pressure, in which condition nitroglycerine, or, preferably, blood-letting will give relief. A child of 10 should receive half the adult dose of ergot, which is a hypodermic syringe-ful of 1 c.c. (15 minims) of a good aseptic ergot. A child of 5, one-half of this dose or $7\frac{1}{2}$ minims; or a proportionate part may be given of the more concentrated form in an aseptic ampul. In 3 hours, if there is no improvement, the dose is repeated, and then once in 6 hours, until there is a decided action. In addition to its sedative action on the nervous system, ergot aids and prolongs the action of the morphine, thus diminishing the dose or curtailing the use of the latter. Only reliable ergot should be used under strictly aseptic conditions. A wet dressing of alcohol in warm water (1:3 or 1:4) will relieve temporary pain and swelling at the site of the injection.

Ice applied to the head and spine is beneficial, or in some instances hot sponge-baths are preferable for relieving internal congestion.

Alcohol and nervous excitants, such as strychnine, caffeine and quinine are contraindicated.

In prolonged coma from pressure, lumbar puncture should be made.

The general care of the patient is the same as in any grave illness—a large, quiet, well-

ventilated room affording access to sunlight, the patient's eyes being shaded or screened, the feet kept warm, the bowels kept open.

As recovery sets in, ergot is discontinued and sodium iodide, in small doses for absorption of exudates, is given 3 times a day, the dose for a child of 5 being not more than 2 grains (0.10 gm.). Iron, in small doses, probably combined with a bitter tonic, is indicated in convalescence.

The patient should remain in bed at least a week after cessation of active symptoms, and should postpone resuming his duties as long as possible. Massage and electricity, at first mild, should be applied to affected joints and muscles. Joint-adhesions should be broken up under chloroform anesthesia.

Normal Serum—The normal serum of the blood has been found of use in the treatment of hemophilia and hemorrhages due to other causes, and has come quite extensively into use. It is administered both orally and hypodermically, and consequently has a place in these pages. In Working Bulletin No. 13, November, 1911, in which Normal Serum is given elaborate discussion, as are the conditions in which it is applicable, is found the following data:

SYNOPSIS.

Normal Serum is that obtained from the blood of normal horses, as distinguished from that obtained from horses undergoing the process of immunization for the production of

curative serum. It has, of late years, come extensively into use as a remedy for hemophilia and other forms of hemorrhage, i.e., hemorrhages from wounds and fractures or following surgical operations. While serum from various animals (horse, rabbit, sheep) has been employed, that from the horse is generally used. The same care in selecting healthy animals and in preparing the serum should be taken as is employed in the production of diphtheria antitoxin.

Normal serum is used hypodermically in hemophilia in doses of from 20 to 30 c.c., or intravenously in doses of from 10 to 20 c.c., to be repeated, if necessary, after an interval of two days.

The dosage by the mouth is from 30 to 80 c.c., in divided portions during 24 hours.

As a preventive of hemorrhage during and after surgical operations, 20 c.c. may be injected the day after operation.

Local applications on saturated cotton may be freely made to oozing surfaces. The technique for hypodermic use is the same as that for injecting curative serums.

ETIOLOGY AND PATHOLOGY OF HEMOPHILIA.

Hemophilia, or hemorrhagic diathesis, means a tendency to profuse or even uncontrollable hemorrhage, occurring spontaneously or as a result of a trivial injury. The hemorrhage may take place from mucous or serous mem-

branes, or from wounds of the skin. The blood may escape into the tissues, into organs, or under the scalp, or into the external genitals. If a cut is made the hemorrhage from the larger vessels is easily arrested, but capillary oozing continues, so that a child who is a "bleeder" must be unceasingly watched and guarded.

The hemorrhagic diathesis is far more common in men. Its existence is rarely suspected until after the first dentition and possibly not until puberty. According to R. C. Cabot, in 70 per cent. of cases it appears before the fifth year.

The disease is transmitted by heredity. It may descend to the off-spring of the mother, who is usually free from the disease but whose father was subject to it. It may not be suspected until the extraction of a tooth or some trivial accident, is followed by persistent bleeding.

The cause of hemophilia is still undergoing investigation. It has been assumed that there is a condition of the blood which prevents coagulation, but according to Da Costa's "Modern Surgery," the blood of the hemophilic coagulates outside the body as well as any other blood.

Emile Weil (*Le Bul. Med.* Oct. 16, 1907), and Dejardin (*Internat. Med. Ann.* 1909; *Br. Med. Jour.* Dec. 12, 1908) agree in regard to the pathology of hemophilia. It is pointed out that the coagulation and formation of fibrin

are due to the action of a ferment contained in the leucocytes on an albuminoid substance, held in solution by the plasma of the blood. These authors hold that in milder forms of hemophilia, the failure of coagulation, to which the symptoms are due, is caused solely by insufficiency or imperfection of the ferment, while in the more severe and inherited form, faulty condition of the ferment is associated with the presence in the blood of anticoagulable material. Some maintain that there is a structural defect in the capillaries, but in a case of hemophilia in the Jefferson Medical College Hospital, in which it was absolutely necessary to amputate a finger because of a crush, a careful study of the vessels of the fingers by Dr. Copeland, failed to show any disease of the blood-vessels.

A suggestive editorial, "Serum Injections in Hemophilia," in the Medical Record, Aug. 8, 1908, p. 239, states: "In the greater majority of cases hemophilia is a hereditary constitutional fault; at times, however, it is acquired. The symptoms of both varieties are similar and well known, and in both the coagulation time of the blood is much retarded. In a recent issue of the *Revue Pratique d'Obstetrique et de Pediatrie*, P. E. Weil differentiates between the accidental, transitory and congenital variety: In the former, he found the blood to be thin and to flow rapidly through a needle inserted into a vein; the leucocyte count was normal, and the coagulation time was seventy-

five minutes, the coagulum being solid and the serum plentiful. In the congenital variety the blood was sticky and flowed slowly; there was an increase in the percentage of uninuclear leucocytes, and the coagulation times was from two to nine hours, the coagulum being soft and the quantity of serum small. Weil found that when three minims of animal serum were added to three cubic centimetres of blood taken from a patient suffering from either variety of hemophilia, coagulation occurred in five to ten minutes. When he injected 10 to 20 c.c. of normal blood intravenously, or 20 to 30 subcutaneously into these patients, he found that the coagulation time was practically normal two days after injection, and remained so several weeks, this effect being a little less marked in the congenital variety. He also found that normal serum applied locally had a styptic action. Weil therefore, advises the injection of normal serum, or, if it cannot be had, diphtheria antitoxin, for the bleeding in hemophilic patients in whom styptics, compresses, ergot, ice, calcium lactate, gelatin, etc., have been unsuccessful."

In the cases of hemophilia neonatorum reported by J. E. Welch (*Am. Jour. of Med. Sci.* June, 1910), the bleeding appeared as a rule during the first week of life, and it occurred very frequently on the second, third and fourth days.

The primary bleeding, as stated by the author, may be entirely in the skin or mucous

membrane surfaces. On postmortem he found that the principal hemorrhage may be in the brain (with extensive laceration) or in the liver, in which case the capsule may be entirely dissected from the surface of the organ; and in addition to these, hemorrhagic spots in other internal organs and effusions of blood in the various serous cavities were found, and in some instances he found the spinal canal filled with blood.

As the author states, the first bleeding may be a slight oozing from the umbilical cord at its point of junction with the skin surface, and not from the end of the cord due to faulty tying. This cord hemorrhage may persist in spite of all local remedies, and in the course of two or three days a considerable quantity of blood may be lost by this apparently insignificant bleeding. Other bleeding may come from the gastro-intestinal tract, as evidenced by the vomiting of blood or bleeding from the rectum. The lips and gums also frequently bleed. Often the severest hemorrhage appears in the skin; and, as a result, large hematomas (blood tumors) may form bearing no relation whatever to traumatism.

Agnew (Da Costa's "Modern Surgery"), reported a case in which hemophilia was limited to the head and neck and there have been cases in which the bleeding occurred from one kidney.

Hahn (Med. Rec. Oct. 8, 1910, p. 624) states that, "Of all the theories concerning the causa-

tion of hemophilia, the most tenable seems to be the one formulated by Sahli—that there is a chemical change in the walls of the blood-vessels. Normally, when the blood-vessels are cut, a substance is secreted by the vessel-walls which causes clotting of the blood and consequent closure of the mouths of the bleeding vessels. But in hemophilia, according to Sahli, this secretion is wanting, thus explaining the fact that hemophilic individuals continue to bleed, although the coagulation time of the same blood outside the body may not be increased. On the basis of this hypothesis, it seems rational to attempt to supply the missing substance by the use of normal serum. This principle in the treatment of the disease is not new. Normal serum has been used in these cases in various ways. It has been given by mouth, subcutaneously and by injection into the bleeding area.”

THE ACTION OF NORMAL SERUM IN HEMOPHILIA.

In discussing the means of preventing hemorrhage in hemophilia and also of protecting those about to undergo surgical operation, DeJardin (*Internat. Med. Ann.* 1909; *Br. Med. Jour.* Dec. 12, 1908) quoted Weil as stating that serum, when added in a dose of three drops to three c.c. of blood of a hemophilic subject, favors coagulation to a marked degree in the inherited form and also in the accidental form of the disease. The subcutaneous or,

preferably, intravenous injection of fresh serum in the subject of the latter form of the disease will be speedily followed by normal coagulability of the blood, and this will persist for about a month. In cases of inherited hemophilia, such injection, though not acting so completely, will favorably modify the anomalies of coagulation.

CLINICAL USE OF NORMAL SERUM.

Wirth (Wein. klin. Woch. 1909, No. 3) has had considerable experience with this treatment, which he reports in detail. In one patient, a boy of 14, known to be a hemophiliac, a persisting hemorrhage from the nose, throat and gums was stopped under application of diphtheria antitoxin locally and injections of from 15 to 20 c.c. No ill effects were observed and the hemorrhagic tendency was kept under complete control for six months. In another case, a hemophilic girl of 15 with metrorrhagia and epistaxis was injected with horse serum, and the uterus and vagina were tamponed with gauze dipped in normal serum; prompt benefit followed.

He has treated 23 patients with hemorrhage from various causes, and is now convinced that the injections of serum are actually an efficient means for treatment. The method is indicated in all affections in which the coagulating power of the blood is reduced, although it may prove effectual in other forms of hemorrhage.

As a rule, 20 c.c. of serum is enough, but 40 c.c. may be injected without harm. The subcutaneous route should be preferred unless the intravenous is urgently required. Normal serum seems preferable, but antitoxic serum may also be applied locally.

Wirth calls special attention to the subsidence of hemorrhages from the skin and mucous membrane in a case of cholemia in advanced cirrhosis of the liver. One new-born infant, bleeding freely from nose and mouth, was treated by local application of sponges dipped in normal serum and the hemorrhage was soon under control. In certain cases of hemorrhages of the lower bowel were arrested by injection of 10 c.c. of normal serum into the bowel.

Emile Weil (Le Bul. Med. Oct. 16, 1907), in a discussion on hemophilia, states that the injection of normal blood serum had given him uniform success in all cases used as a preventive measure in operations and as a curative means to stop bleeding. Seven cases were of spontaneous hemophilia, four having a strong family tendency. The effects of the serum were shown in from twelve to twenty-four hours after subcutaneous or intravenous injection, and lasted for a period of one to two months. Weil says that normal serum exercises a local action in controlling external hemorrhage.

Baum (Mitteil. A. D. Grenzgeb. D. Ned. U. Chir. 1909, xx, 1-20; Muen. med. Wehn. 1909, pp. 56, 834) showed that the addition of fresh

serum, partly deprived of its coagulating power by "hirudin," hastened the clotting in each case "in vitro," but when it had completely lost the coagulating power the addition of serum did not restore such power.

Welch (Am. Jour. Med. Sci. June, 1910), having in mind the almost uniform failure of drugs in hemophilia, decided to attempt the use of normal serum. His first subject was three or four days old. The case was thought to be hopeless by the attending surgeon, who requested his house surgeon to ask permission of the parents for a post-mortem examination. It was at this time the author made the first injection. Ten c.c. were administered subcutaneously three times during the first day, and once each on the following two days. Within a few hours a decided improvement was noted in the condition of the baby; the hemorrhages ceased, and strength returned to the child in a very noticeable way. Within three days it was quite evident that the child was out of danger. The child left the hospital in due time without any signs of having been a bleeding baby.

Encouraged by this result, the attending physicians of the New York lying-in Hospital, placed at the author's disposal for treatment all the bleeding babies that appeared in their wards. Twelve cases were successfully treated, and the author reports eight additional cases. Welch states that the dose of serum to be used depends upon the urgency of the case, but that

one is likely to err on the side of too small doses. It is advisable to begin with at least 10 c.c. and repeat three times a day if the infant is bleeding only moderately. In severe cases it should be given every two hours, and in larger quantities if necessary. It is very important to begin the treatment at the first indication of bleeding. However insignificant it may appear, slight bleeding of the umbilical cord, if not stopped immediately, may be accompanied by fatal internal hemorrhage.

The author states that normal blood serum administered hypodermically gives excellent results in the treatment of tuberculosis, and cites Wright. According to Wright, normal blood serum contains more opsonin than that of a tuberculous person, and Welch believes that normal serum exerts its favorable action by increasing phagocytosis.

DOSAGE.

Dejardin (*Internat. Med. Ann.* 1909; *Br. Med. Jour.* Dec. 12, 1908) states that in adults from 10 to 20 c.c. of fresh serum will suffice for a venous, and from 20 to 30 c.c. for a subcutaneous injection. If it be necessary, a second injection may be practiced after an interval of two days without any bad results. In children half these doses should be used.

Leary (*Boston Med. & Surg. Jour.* 1908, pp. 33, 73; *Am. Jour. Med. Sci.* Nov., 1908) reports a series of 20 cases in which rabbit serum was used in hemorrhage occurring in jaundice in

the newly born and with uterin, typhoid, and purpura cases. In 15 of the patients hemorrhages had already occurred. In the remaining five the remedy was used as a prophylactic measure. The subcutaneous route is preferred for all injections, 30 c.c. being the dose given. He considers his series of cases too small to permit of drawing conclusions, but he pleads for a wider use of the agent under the conditions enumerated in his paper.

USE OF OTHER SERUM THAN THAT OF THE HORSE.

Leary states that the best sources are human blood and the blood of the horse and rabbit. He believes that bovine serum should not be used because, when injected, it is likely to cause symptoms, such as high fevers, rigors, cyanosis, vomiting, and pain in the head and spine. The other serums have not, the author asserts, caused any trouble either immediate or remote.

In three cases of hemophilia, using the dosage suggested by Weil, viz., 15 c.c. of fresh serum for an adult, injecting directly into a vein, or 30 c.c. if given subcutaneously, results were as follows:

In the first case, 30 hours after the injection of 20 c.c. of fresh rabbit serum the blood clotted in a minute, while before, through clotting time was 21 minutes. Fifteen days later the clotting time was again 30 minutes. The other two cases were severe forms of hemophilia in

two brothers, but while the clotting time was reduced "in vitro" the intravenous injections of 10 c.c. of human serum had no influence.

Trembur (Mitteil. A. D. Grenzgeb. D. Med. u. Chir. 1909, **xx**, No. 5) found that subcutaneous injections of fresh serum of sheep and rabbits were of great benefit in a case of severe hemophilia in a young girl where local treatment with tampons and gelatin failed to control the bleeding.

COMPARATIVE VALUE OF NORMAL SERUM AND OTHER AGENTS IN THE TREATMENT OF HEMOPHILIA.

Wirth (Wein. klin. Woch. 1909, No. 3) has found 45 articles on the subject of the internal methods of hemostasis. He reviews them all, with special regard to the use of serum in hemophilia. His analysis shows that the results of gelatin, calcium, strontium, ovarian, and other organ therapy, have been disappointing, although an occasional success has been realized. Far better results have been obtained with subcutaneous or intravenous injection of fresh normal serum, as suggested by Weil.

Bienwald in 1897 reported the arrest of hemophilic hemorrhage by local application of normal human serum. He drew some blood from the child's grandmother and as a last resort filled the wound in the left temple with the blood. The foreign blood coagulated in

the wound, and the hemorrhage was arrested. Twenty cases have been published in which injection of serum more or less completely arrested hemophilic hemorrhage. Only two cases have been reported in which no benefit was derived (Benzani and Mauclair). The effect of the serum does not last over a month. The local action of the serum is also considerable, sometimes rendering repetition of the injection unnecessary.

CHAPTER IX.

Bacterins.

It will not be necessary to go into detail relative to the theory of use of bacterins, or bacterial vaccines, other than to call attention to the fact, as demonstrated by Sir. A. E. Wright, and others, that a certain number of killed, pathogenic bacteria, thrown into the system, will bring about the production of antibodies, destructive to the organisms present. These bacterins, or vaccines, as has been shown by Wright, convert the bacteria present, through the action of opsonins, into such a form as to render them easy of absorption and digestion by the phagocytes. To further the effect of the bacterins, Wright urges the use of sodium citrate, both internally and locally to the site of infection, in that this drug favors the breaking down of the wall thrown about the focus and thus allowing the bacterin-carrying-blood easier access to the point of invasion. The Bier method of induced, or artificial, hyperemia is likewise of use in connection with the introduction of the bacterins, as are massage, incision of the infected area and the applications of hot saline solution.

Primarily the autogenous bacterins, manufactured from the discharges obtained directly from the infected area of the patient, were employed, and this method, where convenient and possible, is followed to some extent at the present time, but, as a rule, the ready prepared, or stock, bacterins are employed, as it has been found that they are relatively active, and frequently are more satisfactory than are those of the autogenous sort. But few physicians are equipped to manufacture the autogenous bacterins, and the cost of manufacture, and the fact that those made in this manner may be contaminated with other than the strain of bacteria desired, and that the stock bacterins are invariably of pure and undefiled strain, make the latter preferable. Time likewise figures. Stock bacterins are always at hand and ready for use at a moment's notice, while it takes several hours to prepare those of the autogenous type, and in some cases this loss of time may work havoc with the patient. In many instances the stock vaccines are employed in the beginning to be followed with the autogenous later on, and in such instances the reports justify the procedure.

In order that the bacterins, or vaccines, may be employed properly, it goes without saying that he who administers them **must know** with what sort of infection, and that absolutely, he has to deal. A strepto-bacterin given in the face of a staphylococcic infection would be worthless; the use of the Neisser-bacterin, in

cases of gonorrhea with mixed infection, while giving some slight reaction, would not be as satisfactory as the Neisser-bacterin mixed. Consequently, in the treatment of the infections by the bacterin method it is of imperative importance that the microscope be employed in the perfection of diagnosis. Because of this fact, bacterin therapy has undoubtedly added much to scientific therapy, in fact, has done much to rescue medicine from the ranks of empiricism. When employed absolutely as indicated, the bacterins become specifics, in that they combat certain known etiologic factors of disease.

Not only have the bacterins a curative effect, in the face of infective invasion, but it has been found that many of them, injected into the healthy individual, serve as immunizing agents, as is witnessed by the success gained through the use of typhoid-bacterin in immunizing against typhoid fever. Such immunity is carried over a considerable period, and in the armies of the world, which have been so immunized, epidemics of this disease do not occur, as was the case prior to immunization. No matter under what conditions the soldiers are placed, the cases of typhoid developing have become a rarity, which was not true prior to the discovery of this method. It is very probable that other infections will be overcome in like manner, as the bacterins become better understood. As there is little, or no danger in the introduction of the bacterins into the

system, they may be employed without fear of untoward results.

In their application the bacterins are injected into those sites, if possible, where the lymph will drain through or past the local lesion, although this is not absolutely necessary, or important. If they enter into the circulation, they will eventually be carried to the site of invasion and be as equally active, as though thrown directly into the infected focus, that is, providing the conditions are such as enable their entrance into such focus. If the suggested use of sodium citrate is carried out, the barriers will be sufficiently broken down as to allow of the entrance of the antibodies, or opsonins, within the site of infection. The theory of dosage is the administration of enough to produce sufficient antibodies to overcome the toxic effects of the pathologic germs present; to increase the opsonins and other antibodies. That bacterins may be active, when administered orally, has been suggested, but not sufficient investigation has been done in this direction as to either substantiate such fact, or to give any idea as to proper dosage. As the hypodermic method has been found sure, in the vast majority of instances, it will undoubtedly continue to be the popular method of exhibition of the bacterins. There is but little, if any, discomfort attending their hypodermic administration, and as they are not destroyed, either in part or whole, when thrown into the subcutaneous tissues, as may be the

case when given by mouth, their ultimate activity is better assured.

It will not be necessary to discuss the method of manufacture of the bacterins at this time, as full descriptions of the method of preparation have been published time and again. The discussion of action of these agents will be taken up as each individual bacterin is taken up and considered.

Acne-Bacterin. Staphylo-Acne-Bacterin—

There are three classes, from a bacteriologic standpoint, of acne. In the first are those cases wherein the comedo is the predominant symptom, in which, in some instances the process has passed on to the pustular and indurated stage. In this class the acne bacillus is the primary infective agent, while the staphylococcus plays a secondary part. The acne-bacterin is indicated in this class.

In the second class, where the induration and pustules are marked; it is found that both the acne bacillus and staphylococcus are practically equally active in causing the inflammatory process. Here the mixed vaccines of the acne bacillus and staphylococcus, or staphylo-acne-bacterin, is indicated. The staphylo-bacterin is indicated in those more acute forms, where there is a greater tendency toward furunculosis, as the microscope shows that the staphylococcus is the chief etiologic factor. In this class, however, the acne bacillus should not be overlooked or forgotten and when found

the acne-bacterin should be added to the treatment.

As a synergist, both the local and internal use of sodium citrate should be remembered, in that this agent favors softening of the wall thrown by nature about the infected area, and allows of the easier access of the blood to the focus of infection, with consequent greater action of the phagocytes and opsonins or other antibodies.

The dose of the acne-bacterin, initially, is from 5,000,000 to 10,000,000 of the killed bacteria. That of the staphylo-acne-bacterin is from 150,000,000 to 300,000,000 of the killed staphylococci and from 25,000,000 to 50,000,000 of the killed acne bacilli. The interval between inoculations is from one to two weeks, and the relative dose is indicated by the existing conditions. The dose should be worked up to that point, the "Negative phase," or rather just failing to meet that point, which is signified by increase of the eruption and feeling of malaise.

The use of the staphlo-bacterin will be considered at greater length, in connection with the treatment of this disease, under the discussion of this vaccine.

Coli-Bacterin—In Working Bulletin No. 1, Third Edition, June, 1911, the coli-bacterin is discussed very fully, and what is said there is repeated as follows:

Mixed Infection—The bacillus coli communis group of affections is especially associated

with diseases of the abdominal and pelvic organs, either alone or in conjunction with some other bacterium, such as streptococcus, staphylococcus, pneumococcus, micrococcus tetrangeous or bacillus pyocyaneus. Among the conditions which are set up which are more or less amenable to vaccine therapy, are peritonitis, cystitis, urethritis, pyelitis and pyelonephritis, endometritis, enteritis, perityphlitis, cholecystitis, subphrenic and hepatic abscess, fistula in ano and even empyema and suppurative periostitis.

Coli-bacterin has been successfully used by Wright (Path. So. Jan. 16, 1906) in the treatment of cholecystitis, acute colon infection of the biliary passages and other colon infections.

Western (Path. So. Jan. 16, 1906) successfully treated cystitis which had not markedly improved under any other treatment.

Allen (Vaccine Therapy and Opsonic Treatment) obtained excellent results in cystitis complicating tuberculosis of the bladder and kidneys and says that the prognosis is almost uniformly favorable in sinus cases, whether coming from the region of the liver, gall-bladder, appendix, pleura or bone, provided that the appropriate surgical measures can also be pursued.

Acute Nephritis and Pyelitis of Pregnancy—The same author states that in acute nephritis, and especially in the pyelitis of pregnancy, recourse should be taken to vaccine treatment when colon bacilluria is present. He also

recommends it in appropriate cases of puerperal septicemia.

Pre-Operative Inoculation—Wright and his co-workers advise the use of coli-bacterin prior to an abdominal operation, where contamination from the infected focus is feared. He also uses it in gonorrheal infection especially associated with the streptococcus and straphylococcus.

Hale White (Pro. of the Roy. So. of Med. 1910, vol. iii) obtained recovery in a case of profound septicemia.

Coli-Bacterin in Gonorrhea—Butler Harris (Pro. of the Roy. So. of Med. 1910, vol. iii) states that simple gonorrheal and colon infection appear to yield very readily after a few inoculations. He reports cures of colitis which had been passing mucus and occasionally blood.

Emery (Ibid) finds that as a rule effects following the use of coli-bacterin in colon infection are marked and immediate.

Inman (Ib.) states that in some cases all of the bacilli disappear from the urine, although the bacilli may persist long after the symptoms have disappeared.

J. C. Briscoe (Lancet, Oct. 30, 1909) recommends bacterin treatment in obstinate cases.

Diabetes—Wright (Practitioner, May, 1908) suggests that diabetes may be caused by a bacterial infection and states that bacterial therapy is indicated in the treatment of these cases.

It has been recommended that the bowels should be thoroughly evacuated, that the urine be made alkaline and that five or ten-grain doses of hexamethylene be employed.

Dosage—Allen (Path. So. Jan. 16, 1906) states that the initial dose should not exceed 50 million and recommends ten-day intervals between doses. In sinuses due to colon infection, a dose of 25 million should not be exceeded.

White and Eyre (Pro. of the Roy. So. of Med. June, 1909, p. 146) used an initial dose of 5 million (autogenous vaccine), four days later a dose of 30 million and ten days later one of 250 million.

Butler Harris (Practitioner, May, 1908, p. 647) finds that a dose of 5 million given a week after the period and repeated a week before the next will often cure slight endometritis with cervical catarrh when the colon bacillus is present. Treatment should be continued at least six months.

Friedlaender-Bacterin—Quoting from Working Bulletin No. 1, we find the Friedlaender-bacterin discussed as follows:

Respiratory Catarrh and Sequelae—Within the past three or four years much study has been given to the bacteriology of catarrhal affections of the respiratory organs. The connection between these catarrhal affections and infections of greater gravity, such as pneumonia, asthma, bronchitis, disease of the middle ear, arthritis, septicemia and the second-

ary infections of tuberculosis, has been definitely established.

Causative Organisms—The bacteriology of colds and respiratory catarrhs has been determined with more or less exactitude. The pioneer workers in this field are Cantley, Dunn and Gordon, Bezancon and De Jong, Prosser White, Cardone, Benham and Allen. The results of their investigations show that the causative organisms in these infections are the bacillus influenzae; the bacillus of Friedlaender and its allies, including, possibly, the *B. proteus*, the *B. Septus* (or *coryzae segmentosus*), the micrococcus catarrhalis, *M. paratetrigenus*, pneumococcus, and possibly the streptococcus salivarius and the staphylococcus.

Friedlaender Bacillus—The bacillus of Friedlaender and its allies are manifest in acute nasal catarrh, ulcerative pharyngitis, and tonsillitis, in chronic nasal catarrh, also in otitis media and sometimes in pneumonia and in abscesses. It has been noticed that the elimination of the Friedlaender bacillus by bacterial therapy may be succeeded by an outburst of infection due to other germs such, for example, as the micrococcus catarrhalis, which has been previously held in restraint. Two or three doses of the appropriate bacterin will in all probability complete the cure.

Chronic Gleet—The bacillus of Friedlaender is also found in chronic gleet. Such cases are usually mixed infections and should be treated as such. Pneume-bacterin and Neisser-bacterin

and even cultures of living lactic acid bacteria have been successfully employed in the treatment of some of these cases.

Dosage—Allen states that the dosage of Friedlaender vaccine depends entirely upon the patient's power of response. According to that author "no upper limit of dosage can possibly be assigned. Thus, until recently, I was afraid to exceed a dose of 500 million of vaccine of the bacillus of Friedlaender. Encouraged by the effects of large doses of staphylococcic vaccine in obstinate cases of acne, I decided to try one billion. In each of three cases, the result was almost immediate cure."

The interval between doses should be three, five or seven days, remembering that the more acute the infection, the smaller and more frequently repeated the dose, and that in chronic conditions the dose should be larger and repeated at longer intervals.

Neisser-Bacterin. Neisser-Bacterin Mixed—Neisser-bacterin is a vaccine made from killed gonococci. It is indicated in those conditions due to the gonococcus invasion, as urethritis, peri-urethritis, prostatitis, vesiculitis, cystitis, epididymitis, orchitis, vaginitis, endometritis, salpingitis, peritonitis, conjunctivitis, endocarditis, arthritis, and in some cases, pleurisy and septicemia.

The recognition that gonorrhea is other than a local disease, and that constitutional treatment is practically invariably required has

paved the way for the use of the bacterins in this disease. Many of the constitutional conditions associated, which in former years failed to show improvement under medical treatment, now submit to application of the vaccines.

The Neisser-bacterin mixed, is a polyvalent vaccine, made from the mixed bacteria found either in the prostatic fluid or pus in chronic conditions, and is employed in combating conditions of the latter class, the mixed infections which occur after the primary action of the gonococcus has disappeared, and where, in many instances that germ is not demonstrable either by the microscope or by culture. In cases of this sort, in addition to the gonococcus, if present, there are to be found the pyogenic staphylococci in the majority of instances, with the streptococci in fifty per cent, while in a lesser number is found the pseudo-diphtheria bacillus.

Irons, in the Journal of Infectious Diseases, June 4, 1908, calls attention to the value of the Neisser-bacterin by the following remarks:

"A typical gonococcus reaction is characterized by a rise in temperature, often only slight; an increase in pain and tenderness in the affected joints, with occasionally some increase in swelling, and a variable degree of malaise. The symptoms follow the injection in from eight to twelve hours, and commonly last about twenty-four hours. Frequently there is a decided tenderness at the site of the injection, greater than occurs after the inoculation

of the same dose of the same preparation in normal subjects. Occasionally there is a marked redness and edema lasting from twenty-four to forty-eight hours. In a case of periurethral abscess of gonococcal origin without secondary infection, which was under surgical treatment with drainage, an injection of 500,000,000 cocci was followed in eighteen hours by moderate swelling and tenderness at the site of needle puncture, and also marked increase in redness and tenderness about the wound. There was no coincident retention of pus or local secondary pus infection to account for the phenomenon, and the wound returned to its normal condition in twenty-four hours. There is usually a slight increase in leucocytosis in the first twenty-four hours after injection.

"The frequency with which these clinical phenomena occurred suggested the possibility of utilizing the reaction in the diagnosis of obscure cases of arthritis in which the gonococcus was the suspected cause. The effects of the injection of dead gonococci into patients not suffering from gonococcus infection were accordingly studied. Eight adults in whom there was no history or sign of gonococcus infection were given injections of 500,000,000 dead gonococci. In none of these cases was there any local change other than that following ordinary hypodermic puncture, and no fever or constitutional disturbance was observed. In a case of pyorrhea alveolaris with

subsequent general infection and painful swellings over the extremities, there was no increase of fever or local symptoms following the injection. A case of gout with active joint involvement showed no local or general changes after a dose of 500,000,000. Leucocytes before injection, 13,200; eighteen hours after injection, 13,000. Temperature was normal throughout. A case of articular rheumatism showed no reaction after a dose of 500,000,000. There was no increase in leucocytosis and the temperature chart showed no abnormal variations. A case of acute arthritis with pericarditis was thought possibly gonococcal in origin. There was no reaction after a dose of 500,000,000. Cultures from the blood and from a small amount of fluid aspirated from the knee remained sterile, and the prostatic fluid contained no gonococci. The subsequent course was typical of rheumatic fever. In four other cases of acute and subacute articular rheumatism there was no reaction after injection of 500,000,000 cocci.

"In a number of suspected gonococcus cases the reaction was of value in making an early diagnosis. A case of monoarticular arthritis with effusion in the knee, in which gonorrheal infection was denied, was given an injection of 500,000,000. The evening temperature, which previously had reached only 100°, rose to 101.8°, and the joint pains increased. The knee was aspirated, and the gonococcus isolated in pure culture from the fluid. A case of chronic

arthritis which had resisted all treatment was given an injection. A slight rise in temperature, with some increase in joint pain followed. The prostatic fluid was found to contain gonococci, and the subsequent course was that of gonorrheal arthritis. A patient who had suffered from extensive gonococcus arthritis had been bed-ridden for one year. There was practically no motion in the knees. After an injection of 500,000,000, the temperature, which for weeks had been normal, rose to 99.5° , and the patient complained of malaise and increased pain in the joints. A patient with aortic aneurism who denied gonorrheal infection, had been selected for control experimental inoculations. After an injection of 500,000,000 cocci, the temperature, which had been uniformly normal, rose to 100°F. without any other apparent cause, returning to normal the next day, without any subsequent rise. The prostate was examined and found to be large and somewhat tender, and the secretions contained numbers of leucocytes with typical intracellular gonococci.

“The reliability of the clinical gonococcus reaction as a diagnostic procedure will be determined only after many tests. It has many points in common with the tuberculin reaction, and similarly too there may well be cases of gonococcus infection found which do not respond. It appears, however, to be well worth a trial. Should the reaction prove to be reliable, a valuable and much needed aid will be at

hand for the diagnosis of obscure joint, synovial and periosteal diseases."

Aronstam (J. A. M. A. Oct. 24, 1908) says that while the Neisser-bacterin may cause a recrudescence in dormant gonococcic arthritis, probably acts materially to shorten its duration.

The necessity of using the mixed bacterins in chronic conditions is observed by von Notthafft (Die chron. Gon. der mann. Harn. und ihre Kompl. II verm. und verb. Auflage, Leipzig, 1910. First Edition, Part 3, p. 137) as follows:

"1. Already in the second half year after infection the gonococcus is demonstrable in the prostatic secretion in no more than 73 per cent. of the cases. This figure follows in the third half year of 50 per cent., in the fourth to 18 per cent., in the fifth to 6 per cent. From the end of the third year on, the gonococcus can no longer be found in the prostatic secretion.

"2. Already in the second half year other bacteria than the gonococcus appear in the prostatic secretion. In the fourth half year pure gonococcus infections are no longer demonstrable."

Dosage—In the ~~discussion~~ of this part of the question, it ~~seems~~ to be the consensus of opinion ~~that~~ it should be based upon the ability of the patient to bear the effect of the Neisser-bacterin. It should be realized ~~that~~ toxic conditions are liable to follow large doses, especial-

ly of freshly prepared bacterin, and that the former large doses of 100,000,000 to 500,000,000 are liable to produce undesirable effects. The dose suggested today ranges from 1,000,000 to 5,000,000 initially, this to be increased or decreased, according to effects produced. In some instances the smaller dosage is never increased from the beginning, while in others, in order to obtain satisfactory results a marked increase is necessary. If a large dose has been injected and bad results follow, in so far as symptoms are concerned, no real harm should follow, but the next injection should be smaller and the latter not increased as long as there is improvement in the condition. The undesirable effects are aggravation of the symptoms, rise in temperature, malaise, etc., which show a toxic dose has been given.

In the administration of the Neisser-bacterin mixed, the method is to inject primarily a mixture containing 100,000,000 each of staphylo-aureus, staphylo-albus and staphylo-citreus, and 50,000,000 each of streptococci, bacillus coli, pseudo-diphtheriae and gonococcus, which may be increased or diminished, the condition of the patient giving the indication. No increase is necessary or desirable, if there is improvement. If there are symptoms of a decided negative phase, the following dose should be reduced. The interval between injections is from 5 to 7 days, and here again does the condition indicate as to whether the interval should be shortened or lengthened.

Neoformans-Bacterin—It is believed by some, and disputed by others, that the *Micrococcus Neoformans*, is the cause of cancer. Recently a vaccine, known as neoformans-bacterin, has been offered. Relative to the organism, and the bacterin prepared therefrom, we find the following remarks in Working Bulletin No. 1, Third Edition, June, 1911:

Micrococcus Neoformans and New Growths—Doyen, a French surgeon, isolated from new growths a micrococcus which he believed to be the specific cause of cancer, and which he named neoformans. This work Doyen did not make public for ten years, as he believed medical science was not ready to accept anything so advanced.

While the work of other investigators seems to disprove the theory that this micrococcus may itself be the cause of cancer, it is believed by many that the micrococcus neoformans is frequent cause of intercurrent infections.

Ulcerative Cancer—This micrococcus is found in a large proportion of malignant new growths, especially those which have ulcerated. The effect of these ulcerations is to frequently aid the cancerous growth by so weakening the tissues that the malignant growth is able to spread more rapidly.

Arguing from this point, Wright and others have made use of a neoformans vaccine for the treatment of ulcerated cancerous conditions, with sometimes remarkably beneficial results.

Restricted Uses—When one has seen a num-

ber of cases in which there has been marked benefit following the use of a certain remedy, it is difficult not to become enthusiastic and believe that equally good results would be obtained in all other cases with the remedy. In probably no disease has this condition been more true than in the treatment of cancer. Neoformans vaccine will benefit patients suffering from some forms of malignant new growths, but it is too much to claim that the vaccine will cure cancer or that even benefit can be obtained in every case. If this claim is made, some notable failure will cause the vaccine to fall into unearned disrepute.

Neoformans Serum, Mixed Infection—A Paine and D. J. Morgan (Lancet, April 7, 1906) review Doyen's theories as to the occurrence of his so-called "micrococcus neoformans" in malignant growths, and the various steps leading up to the elaboration of his serum. Of nine cases treated by them with serum injections, no effect on the course of the disease was noted in four. In two, the injections were followed by severe pain, and in three by severe constitutional disturbances. Concerning the micrococcus neoformans, the authors note that it is often present with other micrococci in malignant tumors but in their opinion not in sufficient numbers or with a constancy to enable it to be regarded as the etiological factor in the evolution of these growths. In their hands, the inoculation of animals with this organism has been followed, not by the

formation of neoplasma, but by the expression of inflammatory reactions.

Cancerous Cachexia—C. Jacobs and V. Geets believe that there exists in cancerous cachexia, a specific micro-organism, the micrococcus neoformans of Doyen, and report cures from its use. They summarize their results in 46 cases as follows: "Cure," maintained after several months, 7; lasting improvement, 12; transient results, 7; no results, 12; still under treatment, 9.

Dr. Alexander J. Anderson, of Newport, R. I., published in the American Journal of Dermatology, a report of a case of carcinoma of the kidney which improved under the use of neoformans vaccine. The case was still under treatment.

Accessory Treatment—It should not be forgotten that Doyen uses fulguration and other methods of treatment in conjunction with his vaccine therapy; and furthermore, that the exact nature of the neoformans vaccine employed by him has never been published.

Dosage—The initial dose of neoformans-bacterin is given as 25 to 50 millions.

CHAPTER X.

Bacterins.

(Continued)

Antipneumococcic Serum (Anti-Pneumonic Serum). Pneumo-Bacterin. Pneumo-Bacterin Mixed—As both antipneumonic serum and the pneumo-bacterin and pneumo-bacterin mixed as employed in the treatment of pneumonia, and pneumonic infection, and as each has its place, they will be considered under one head.

As the information contained within Working Bulletin No. 7 has been gathered from all sources, impartially, this will be quoted to a considerable extent in the discussion of these agents.

Pneumo-Bacterin—This is a suspension in sterile physiological salt solution of the bacteria secured from 24-hour agar cultures of the pneumococcus (Frankel). The microorganisms are rendered sterile by subjection to a temperature of 60°C. for one hour. The suspension is standardized by bacterial count and diluted so that it contains approximately a fixed number of pneumococci per cubic centimeter. A small percentage of trikresol (0.25 per cent.) is added as a preservative.

Polyvalency—The cultures used in preparing bacterins contain bacteria originally obtained from a large number of infectious patients. Many species of bacteria comprise numerous subvarieties or strains. There may be but little apparent difference microscopically, yet biological experiments show different reactions which indicate that the rule of specificity obtains, at least to a certain extent, even in these minor subdivisions. It is principally for this reason that autogenous bacterins (those made from specimens secured from the patient to be treated) were at first thought to be essential. Later experience has demonstrated that the preparation of autogenous bacterins consumes so much time and expense as to make them in many cases both useless and unavailable. Stock bacterins, on the other hand, composed of cultures of bacteria secured from numerous patients and comprising as many strains as possible (or polyvalent) have produced most satisfactory results. The use of autogenous bacterins may be said in general to have found its proper place as a form of treatment in obstinate or chronic cases where the stock bacterins have been tried without satisfactory results. Even in these cases the lack of efficiency of the bacterin may perhaps in many instances be attributed to the inability of the antibodies to reach the part affected, improper dosage, inaccuracy of diagnosis. In many cases the employment of artificial hyperemia, etc., may bring about the results desired.

Theoretical Considerations Relative to Bacterin Therapy—Bacterin (vaccine) therapy in general is based upon Wright's opsonic theory of immunity. According to Metchnikoff's teachings bacteria which gain entrance into the blood or tissues are destroyed chiefly by the phagocytes. Wright demonstrated that before this can occur the bacteria are acted upon by certain bodies in the blood, which he called "opsonins." These are specific (i.e., a pneumococcus opsonin will attack only that microorganism and not other bacteria), and are formed under the stimulus of the presence of bacteria or their products of metabolism. By means of the "opsonic index" it may be shown that with the increase or diminution of the specific opsonin content of the blood the phagocytic power of the leucocytes is correspondingly increased or diminished.

Artificial Stimulation of Opsonic Production—Holding the view that opsonic bodies are formed by a protective reaction of the fixed cells to the attacks of parasitic microorganisms, Wright developed a method of artificially increasing the specific opsonic content of the blood by injecting into healthy tissues bacteria which have been rendered incapable of multiplication, i.e., "killed bacteria." The formation of opsonins is thus stimulated and the "killed bacteria" are consequently ingested by the phagocytes. The body cells, however, produce opsonins greatly in excess of the quantity necessary for the destruction of the sterile

microorganisms present at the site of injection, and the surplus enters the blood and other body fluids and increases their specific opsonic content.

Opsonic Production in Spontaneous Recovery—The initial attack of most infections is of a local nature. This is followed by multiplication of the bacteria and destruction of tissue, and in some cases the flooding of the body fluids with bacteria and bacterial toxins on one hand and increasing migration of phagocytes and the formation of opsonins and other antibodies on the other. The growth of the bacteria under favorable circumstances may be for a time much more rapid than the formation of antibodies, and a severe illness ensues. Great destruction of tissue may take place as well as general intoxication from the absorption of decomposition products and toxins. But when spontaneous recovery occurs, the production of antibodies proceeds steadily, and, it would seem, with increasing rapidity, until finally a time is reached when there are sufficient opsonins and other antibodies to enable the phagocytes to overcome the bacteria completely and to neutralize their toxins. Thus it becomes evident that if during the early stages of a disease the formation of antibodies in some healthy portion of the body is artificially induced, and these are carried to the infected area, rapid destruction of the bacteria will take place and the disease process aborted.

This, in fact, constitutes the basis upon which

the theory of bacterin, or vaccine, therapy rests. In the words of Wright, it consists in exploiting "in the interest of the infected tissues the unexercised immunizing capacity of the uninfected tissues."

Active Immunization in Treatment—Employing Wright's "opsonic index," which is simply a comparison of the relative phagocytic power of the specimen of blood being investigated (under test) with that of normal blood, it may be shown that in a person already suffering from an infection, an injection of killed bacteria of the same species as that producing the disease causes immediate temporary reduction of the specific opsonic content of the blood. This is called the opsonic negative phase. It is followed, however, in a very short time by an increased opsonic production, which continues until it has reached a point considerably above that originally present. This is known as the opsonic positive phase. While the occurrence of the opsonic negative phase is not necessarily accompanied by a corresponding clinical aggravation of symptoms, when the opsonic positive phase sets in a distinct improvement in the condition of the patient is usually observed. After the opsonic positive phase has reached its height the opsonic content of the blood gradually diminishes. At this time another injection of bacterin is indicated. The procedure is then continued until a cure of the primary infection is obtained.

Dosage and Method of Administration—In

treatment according to Wright, the production of a clinical negative phase should be avoided. The success of the treatment depends, indeed, to a great extent on the careful regulation of dosage and the ascertaining of the maximum dose tolerated without ensuing clinical negative phase, i.e., aggravation of symptoms, rise of temperature, chills, and a general feeling of malaise. Aside, however, from the necessary reduction of dosage, together with the possible psychic effect on the patient, no harm from the occurrence of the clinical negative phase has been recorded. In fact, in some obscure chronic affections it has been deliberately produced for diagnostic purposes.

Fortunately the extensive use of bacterins has developed what may be termed an average range of dosage. The use of the opsonic index, at one time considered the only means of properly controlling the dosage, but which is a troublesome and time-consuming procedure, has been almost entirely dispensed with and in most cases reliance is placed upon clinical observation for the control of dosage. If the patient steadily improves with a repetition of the initial dose no increase in dosage should be made; when improvement is slow or absent the dose should be gradually increased.

A careful review of the literature shows a change in opinion regarding the dosage of pneumo-bacterin. The initial dose first recommended was usually 25 million killed bacteria, and that this first dose be gradually increased

until the desired results are secured. Leary, of Tufts Medical School, commenced with doses of 10 million administered every 3 hours, but soon changed to 100 million every 24 hours. Robertson and Ilman employ doses ranging from 25 million to 600 million and state that the results seem to be more definite with the larger doses. Rau found the usual dose of 10 million to 50 million too small and also advocates the larger doses. He begins treatment with a dose of 50 million, followed in 24 hours, if necessary, by 100 million, while in some cases 150 million are employed.

It should always be borne in mind that greater relative benefit may be secured by early treatment. Obviously the destruction and alteration of tissue caused by the bacteria or by their products, and the exudates often present after the disease has progressed for some time, may prevent the antibodies from reaching the point of infection and thus render them comparatively useless. This, however, may be to a great degree overcome in some cases, especially in infections of the joints, etc., and chronic empyema, or when there are areas of consolidation remaining after active infection has subsided, by manipulation and other mechanical methods of producing local hyperemia, or by the use of medicaments which have the property of lessening the viscosity of the blood e.g., citric acid—40 gr. internally.

Chronic Cases and Localized Infection, Due to the *Pneumococcus*—Pneumo-bacterin may

be employed, with success, in other infections than pneumonia, such as arthritis, ulcus serpens, pyorehea alveolaris, and others in which it is possible to demonstrate the pneumococcus as the means of infection. These will be considered at length under the head of "Clinical Reports."

Pneumo-Bacterin Mixed—Is prepared and standardized in the same manner as pneumobacterin, but is composed of several varieties of pathogenic microorganisms and is intended for the treatment of combined infections due to the pneumococcus, streptococcus and staphylococcus.

Indications and Use—In practically all cases of broncho-pneumonia mixed infection is present. Therefore, treatment with a bacterin composed of only one organism is not likely to be efficacious. For this reason a bacterin which contains all the varieties of pathogenic bacteria found in a large number of cases is employed, and has proved of great value in both treatment and prophylaxis. It was previously considered necessary in mixed infections to have the bacterin prepared from the patient (auto-genous bacterin). This procedure is necessarily slow, and is now the general practice to employ a mixed bacterin under the guidance of such indications as may be clinically observed or which may be elicited by bacteriological examination. Mixed bacterins have also been very successfully employed in the immuniza-

tion of persons subject to recurrent attacks of respiratory infection.

Characteristic Clinical Symptoms Produced by the Presence of Various Organisms in the Respiratory Tract—Allen (Jour. Vaccine. Ther. July, 1912) gives the following symptomatology for the early differential diagnosis of infections of the respiratory tract:

Pneumococcus—This microorganism is capable of involving each and every portion of the respiratory tract, with rawness of the mucous membrane, harsh and dry cough. By the second or third day the infection has begun to spread upward into the nasopharynx and down into the trachea; on the third and fourth day the pharynx and trachea may feel sore, while expectoration and nasal discharge becomes profuse and mucopurulent. There is considerable malaise and headache and some rise in temperature. Involvement of sinuses follows, with a sense of fullness and referred head pains, with extension to chest, and moist sounds in the bronchi and bronchioles, and muscular or pleuritic pains. Finally, the alveoli are attacked and definite pneumonia sets in. The symptoms may, however, vary on account of the fact that the first attack may be located at any part of the entire respiratory tract.

Bacillus Septus—Dryness or tickling of soft palate, extending in 24 hours to the nasal mucosa, with sneezing and discharge of this mucus. The pharynx next becomes involved, causing pain in swallowing, and loss of smell

and taste. Headache, malaise and pyrexia are slight. The acute stage subsides in 3 or 4 days, while the subacute stage persists, characterized by thick but not very purulent mucus, for about 4 days.

Micrococcus Catarrhalis—Attacks any point of the entire respiratory tract, producing any form of inflammation from a nasal catarrh to a capillary bronchitis. There is usually an inflamed feeling of the fauces and nasopharynx, which is quickly followed by extension into the nose and pharynx. There is a thin, profuse discharge from the nose, and thin, colorless watery mucus from the larynx, impairment of voices, cough, and sore feeling in the trachea. Deafness exists, the sinuses are usually infected, and there is a sense of fullness. Toxic absorption produces headache, malaise and rise in temperature. The subchronic stage commences in 3 or 4 days, and may be present for weeks. Profuse mucopurulent mucus may be expelled. The lower respiratory passages may become involved with the production of a troublesome and persistent but not very acute infection of the bronchi and bronchioles; copious thin, but very tenacious or purulent mucus is voided. Infections by this organism have a tendency toward chronicity or to occur frequently. At times they very closely resemble infections by *B. Influenzae*.

Micrococcus Paratetrageus—The symptoms in this infection may resemble closely those of *Micrococcus catarrhalis*, but the favorable

point of attack seems to be the larynx. There is usually huskiness of voice, followed by in 1 or 2 days by a dry, paroxysmal cough, with expulsion of very small bits of clear, tenacious mucus. The secretion is not profuse or mucopurulent. As a rule, there is no involvement of the accessory sinuses. The chief characteristic is a dry, hacking cough.

Friendlander Group—The nasal passages and adnexia are first attacked, causing sneezing, malaise, slight headache and loss of smell. The discharge is profuse, usually clear and colorless; and when the antrum or sinuses have become involved it is mucopurulent. The eustachian tube usually escapes infection, and subjective noises and deafness do not occur. The sore throat and cough are absent. In rare cases, in adults, but more commonly in children, the bacillus may find its way to the bronchi and set up bronchitis or broncho-pneumonia. These infections are likely to become chronic.

B. Influenzae—Is usually associated with the pneumococcus. There is extreme malaise, headache, joint-pains, pyrexia, perhaps rigors. Digestive disorders follow, and neuritis, diffuse or local; or herpes zoster may appear; in such instances the infection is probably systemic and may become latter localized in the pulmonary tissues.

CLINICAL REPORTS.

Pneumonia—Robertson and Illman (Penn. Med. Jour. Jan. 1912) give data in regard to 50 cases of pneumonia, 30 of which received only customary treatment and 20 of which were given bacterin injections. "Of the 30 cases not given bacterins, 12 died, or 40 per cent.; of the 20 to whom bacterins were given 3 died, or 15 per cent.; or excluding a woman who died of uremia the mortality in the 19 cases was 10.5 per cent." The doses employed ranged from 25 million to 600 million. Results seemed to be more definite with larger doses.

Leary (Dental Cosmos, 1910, vol. iii), after three year's experience in the use of bacterial vaccines, began an investigation of pneumo-bacterin in pneumonia. An appeal was made to several medical groups to test the value of bacterial therapy. The total number of cases was 83, eight patients died (9.7 per cent.) (usual death rate, from 20 to 25 per cent.); 34 of the cases occurred in alcoholic pneumonia, 6 of whom died (17.7 per cent.). Previous death rate from alcoholic pneumonia, 41 to 53 per cent. In 8 cases the crisis occurred on the third day.

The author advises the early administration of pneumo-bacterin. The bacterin treatment should be employed "the moment a diagnosis is established. A full dose should be injected of from 10 to 50 million, progressively increased in acute cases, every 4 to 8 hours."

Morgan (Pro. Roy. Soc. of Med. vol. iii, No. 9, Sup. p. 5) treated 43 cases of pneumonia with pneumo-bacterin (some of the cases were treated with stock bacterin and some with autogenous). In many of the cases he administered doses of 50 million of the autogenous bacterin without any harm, but he believed that doses of 15 million to 30 million would usually give the best results. In the cases reported where an artificial crisis was not produced the temperature fell by lysis with marked improvement in the symptoms. Morgan points to one of the most noticeable features as being an improvement in the general condition even without much change in the temperature. The patient is relieved, sleeps easily, and the appetite is improved. If there is a fall in temperature soon after the bacterin is administered, which sometimes occurs in as short a period as one to two hours, another dose is indicated when the temperature rises again. If there is no change in twenty-four hours the dose should be repeated. He finds the opsonic index frequently unreliable as a guide to the progress of immunity in pneumonia.

Harris (Br. Med. Jour. June, 1909, p. 1530) finds that a dose of 20 million to 50 million killed pneumococci may be given without harm, and is generally followed by a fall of temperature within a few hours. The temperature usually rises again, but not to its previous level, and he found that it is necessary to repeat the inoculation several times. He advises the early

use of the bacterin. He considers that every severe case of pneumonia should be regarded as possibly a fatal one, and suggests that the bacterin be employed as early as possible.

Ager (*L. I. Med. Jour.* 1910, vol. iv) reports the case of a girl of nine who had been ill for 19 days with lobar pneumonia. The circulation had been so bad that death seemed imminent. On the 20th day a mixed bacterin containing 20 million pneumococci, 10 million staphylococci, and 10 million strophococci, was injected. A marked improvement was noticeable within a few hours. Two days later an increased injection (30 million pneumococci, 30 million staphylococci, 15 million streptococci) was given. The patient made a rapid and uneventful recovery.

Craig (*Med. Rec.* Nov. 18, 1911) reports treatment with pneumo-bacterin of 20 cases among old sailors, all over 60 (some 80-90 years old). Most were alcoholics, nearly all had chronic nephritis, arteriosclerosis, and dilated hearts. The average death rate in the institution for the preceding five years from pneumonia had been 66 per cent. Yet of the 20 only 4 died, a death rate of 25 per cent., and of these 4 only 1 died directly from the pneumonia, this being a very severe case of bilateral disease; of the 3 other cases 1 was already complicated by purulent pericarditis, and another by acute uremia and acute dilatation of the heart.

Sinclair (*Med. Rec.* Feb. 10, 1912) reports

6 cases in which the first injection of pneumo-bacterin was given within 48 hours after the initial chill; one patient was an infant of 22 months. Two cases in which the infecting agent proved on culture to be the pneumo-bacillus of Friedlaender were not influenced. One of these went through the following course: Lobar pneumonia, appendicitis (operated); pleurisy (operated); alveolar abscess, arthritis, peritonitis, death from exhaustion, but with original infection. In patients treated later than 48 hours after the initial chill the disease was apparently unaffected, but no complications developed. All recovered.

Raw (Lancet, Mar. 9, 1912) reports 207 cases of pneumonia treated by pneumo-bacterin injection within two years, with a death rate of a little over 16 per cent. He emphasizes the fact that to be of real value the bacterin must be injected early in the illness; in fact, he states "if it can be used on the first or second day it acts at times almost miraculously." After the fifth or sixth day when there is a general bacteremia the bacterin seems to exert little or no influence on the course of the attack.

He thinks the usual dose of 10 million to 50 million killed bacteria too small, and found that to get the full effect of the bacterin it is necessary to give larger doses. The practice in the cases treated was to begin with an initial dose of 50 million, followed in 24 hours, if necessary, by another injection of 100 million,

and in some cases even 150 million were employed. As a result of a large experience the author is convinced that the bacterin in itself is harmless, and he has never noticed anything but good effects from its use. In a certain proportion of cases it appears to have no effect either one way or the other; on the other hand, in a great many cases injection of a large dose is followed by a feeling of comfort and relief associated with a rapid fall in the temperature. There is frequently a drop of one or two degrees after a large injection of bacterin, but the temperature rises again, or until the true crisis appears. It is apparently necessary that before the crisis occurs antipneumotoxin should be formed in the blood in sufficient quantity to neutralize the pneumotoxin. The effect of the bacterin on the pulse is always good, reducing it frequently in an hour by 30 to 40 beats.

Delayed Resolution—Coleman (Roy. Acad. Med. Ireland, Mar. 2, 1906) reported a case of unresolved pneumonia of 30 days' standing; 2 injections of 45 million pneumococci, given at intervals of 16 days, brought about a complete resolution.

Briscoe and Williams (Practitioner, 1908, p. 675) conclude that in the more or less acute conditions following lobar pneumonia, the bacterins cause marked improvement in the general condition. The effect of each injection is stimulating and the patient appears more

cheerful afterwards. In children the injections were followed by rapid increase in weight.

Empyema.—Floyd and Worthington (Boston Med. and Surg. Jour. 1908) report 2 cases of pneumococcic infection treated with bacterins as follows: a girl of 2 years had complained of 8 days of pain in the right side. The day before admission to the hospital an abscess opened on the front of the chest and it was found necessary to resect a portion of the eighth rib. The child was weak and thin and in a precarious condition. As a culture from the discharge showed pneumococci, a stock of bacterin containing 500 million pneumococci was injected and 2 days later the opsonic index had risen from 0.6 to 1.17; the next day the index was 2.25 and the following day 50 million bacteria were injected. The child showed marked signs of improvement and was much stronger. Two days later 50 million were again injected, and after this inoculations were continued regularly. The child gained rapidly and after 3 weeks was discharged from the hospital in excellent condition, the sinuses all healed.

A boy 3½ years old entered the hospital with a history of pneumonia followed by empyema. A portion of the eighth rib was resected and a collection of pus evacuated. Diagnosis of pneumococcus infection. An injection of 50 million pneumococci was made and similar injections were continued every 3 days, as improvement followed every dose; three weeks

later the sinuses were almost closed and soon the child was sent to the country entirely cured.

Septic Infection.—Betham Robinson (Br. Med. Jour. Mar. 13, 1909) reports a case of primary diffuse peritonitis caused by the pneumococcus and treated with bacterin. Owing to a diagnosis of appendicitis, the abdomen was opened and the localized abscess drained. A pure culture of pneumococcus was obtained from the pus, and five days after the operation, as there was a rise in the temperature and in the pulse, treatment with bacterins was instituted. The patient received at intervals of five or six days, eight injections of ten million to 25 million pneumococci. After the first two injections there was a fall of temperature. The wound later became infected with staphylococcus and it was necessary to make a counter-opening for improved drainage before healing occurred.

Jowers (Practitioner, Sept., 1908) reports a case of peritonitis due to pneumococcus infection of the tube; three injections of 50 million, 60 million and 200 million respectively were given 8, 10 and 13 days after an abdominal section. The patient recovered, but the author believes recovery would have been more prompt if treatment had been commenced immediately after operation.

Putnam (Bost. Med. and Surg. Jour., 1908) reports from A. E. Wright's clinic a case of abscess of the antrum of Highmore which was

caused by pneumococcus and was treated by the bacterin of this organism. Two inoculations at an interval of seven days resulted in complete cure.

Arthritis Deformans.—Beebe and Medalia (Bost. Med. and Surg. Jour. 1908) report of a case of arthritis deformans in which the opsonic index to various organisms was taken repeatedly. As the index to pneumococcus was always found to be low, they decided to experiment with bacterins of this organism. Stock bacterins were used, beginning with a dose of 100 million. Soon afterward the pain disappeared, although it had previously been necessary to keep the patient under the influence of morphine. They do not say how many doses were administered, but eventually the swellings about the joints were remarkably reduced and the patient was able to go about alone. The index rose above normal and remained high. They also report a case of mixed infection in which staphylococcus infection had been grafted on a pneumococcus infection, causing empyema in the right chest, which had been operated on and drained a year before. The opsonic index was found to be low to both staphylococcus and pneumococcus. It was not possible to get a good growth from pneumococci secured from the patient and for this reason stock bacterins were used. After three injections of 250 million staphylococci and 100 million pneumococci, the discharge had almost ceased. During the next two months the doses were gradu-

ally increased in size to 1500 million staphylococci and 250 pneumococci, and were given every two weeks. After one of these large injections, and presumably as a result of it, there was reinfection with a reopening of the sinuses and a free discharge of pus, the indices remaining above normal. The doses were, therefore, decreased to 250 million staphylococci and 100 million pneumococci, and a few injections brought about a complete and permanent cure.

Ulcus Serpens.—Allen (Practitioner, 1909, p. 737) reports a series of cases in which bacterin treatment was successfully employed in diseases of the eye. Two patients with *ulcus serpens* of the cornea were among those receiving treatment. In one of these cases excision was apparently the only remedy. Despite the fact that the opsonic index was already 2.5, an injection of 250 million organisms was given. Within three days improvement began and three days later a similar dose was administered; 18 days after the second injection the index was 6.3 and the inflammatory process had quite subsided. In another case one eye had already been removed for chronic ulcerative keratitis with shrinkage of the globe; 18 months later the second eye was attacked and grew steadily worse until vision was confined to the perception of a bright light; four injections were given, two of 200 million and two of 500 million. Two months later the eye was free from inflammation and the vision improving. three other cases of the same nature which

seemed entirely hopeless were also treated with most satisfactory results. "The favorable result obtained in these cases was largely due to the bacterin treatment, and but for it the first-mentioned patient would undoubtedly have lost his eye." Autogenous vaccines were employed in these cases.

Allen (Vac. Ther. and Ops. Treat. Phila., 1908) also reports three cases of perforating ulcer of the cornea with hypopyon, in which the eyes were apparently saved by the use of bacterins in doses of from 175 million to 600 million.

Pyorrhoea Alveolaris.—Goadby (Lancet, 1909, vol. 1, p. 52) reports 47 cases of pyorrhoea alveolaris treated with bacterins. Of these cases 36 were cured; that is all the general symptoms—*anemia, toxemia, weakness and chronic intestinal dyspepsia*—cleared up, together with the local suppuration. Nine of these cases were relieved; that is to say, the general symptoms disappeared, although the local discharge remained.

In taking cultures from the pus in order to determine which organism is the causative agent, he found the ordinary streptococci of the longus type. The pneumococcus was found at times, but streptococcus was more common. The micrococcus catarrhalis was commonly present, but probably was not the responsible organism. It was generally associated with streptococci or staphylococci. Constitutional disturbance rarely occurred after injection, but

in a few cases when the opsonic index was abnormally low the first two or three injections were followed by vomiting, acute headache and general malaise.

Leary (Dental Cosmos, 1910, vol. iii, p. 52) in an article on the bacteriology of pyorrhoea alveolaris, states that he has studied about 100 cases of pyorrhea, and has found a great variety of organisms. His most constant finding has been the pneumococcus, and he believes that Goadby's failure to differentiate this organism was due to the fact that his primary cultures were made upon agar, on which the pneumococcus does not grow readily. The streptococcus longus and brevis appeared frequently. Staphylococcus was common, but usually associated with pneumococcus or streptococcus. The fusiform bacillus of Vincent was almost always present. This organism is a normal inhabitant of the mouth, and only occasionally become pathogenic. It is probable, however, that in many cases it is of importance in producing disease in individuals whose vitality has been lowered.

As pneumococci and streptococci were found most frequently and the staphylococci were commonly associated with them, he has used in the bacterin treatment of these cases a stock pneumo-bacterin to which has been added a stock strepto-bacterin and often a stock staphylo-bacterin. The results are distinctly encouraging in mild cases when pus was not abundant; in this treatment combined with the use

of Lugil's solution locally it has repeatedly given perfect satisfaction. In pus cases it has ended almost equally well. When teeth are greatly loosened their perfect reestablishment in the socketing has been slow, and some teeth have had to be sacrificed. The healing of retracted gums and the obliteration of pus-pocket leave the joints between the gums and the teeth less perfect than they were originally; that such joints will remain perfectly free from infection is almost too much to expect.

Medalia (Bost. Med. and Surg. Jour., 1910, vol. clxii) has been experimenting for some time with the use of bacterins in the treatment of pyorrhoea alveolaris. He finds in 90 per cent. of his cases a pure pneumococcus infection with which staphylococci and streptococci are more frequently associated than other organisms. A large percentage of cultures taken from the gums of normal persons showed the presence of the same organisms as those found in the discharges from pyorrheal affections. The injury to the mucous membrane from concretions around the teeth renders it liable to infection from these bacteria. The opsonic index was always found low to the pneumococcus, slightly low to the staphylococcus, and normal to other organisms. The injections ranged from 30 to 150 million pneumococci, combined with from 150 to 500 million staphylococcus aureus bacterin.

He has had 33 patients under treatment, 11 of which are entirely cured; five of these have

remained over a year without any recurrence. All of the others have shown great improvement, such as disappearance of pus, loose teeth becoming firmer, gums regaining their pinkish color and elasticity, and, when present, pain practically always relieved. Patients suffering from pyorrhea who are also troubled with rheumatic pains in the joints and muscles have shown great improvement in their rheumatic symptoms at the same time that their local condition has improved.

Pneumococcal Vulvovaginitis. — Chappelle (Lancet, June 12, 1912) reports two cases of pneumococcal vulvovaginitis in children. Clinically the condition could not be distinguished from other forms of vulvovaginitis.

The exact nature was recognized by bacteriological examination. The following treatment was employed: For a few days the child was kept at rest, and the parts bathed at frequent intervals with a warm antiseptic lotion. An autogenous bacterin of five million pneumococci was given. The acute nature of the inflammatory process rapidly subsided, and then warm vaginal douches of zinc permanganate were given under low pressure.

The inflammatory process did not spread further than the vagina, and in ten days the discharge was almost gone, but pneumococci were still present in the vagina. Consequently another dose of vaccine of five million was given and local treatment was continued. The condition cleared up rapidly, requiring only

four doses of vaccine in all. Had the patients been adults probably the external os should first have been plugged, to prevent possible ascent of organisms during the douching process. Recently pneumococcal peritonitis has been found to be not at all uncommon in girls. To those believing that the path of infection may be an ascending one by way of the Fallopian tubes, these cases will be of interest. The importance of ascertaining the exact nature of the vaginal discharge should therefore be strongly emphasized.

Antipneumococcic Serum.—Passive Immunization, or Serum Therapy.—When an infection has extended to numerous points beyond the original focus, and the bacteria or their products are present throughout the blood and tissues (bacteremia, septicemia or toxemia), attempts artificially to induce the formation of antibodies may be unsuccessful. In these cases it is necessary to resort to the injection of the specific opsonins and other antibodies found in the blood of animals which have been actively immunized against the pathogenic organism causing the disease. This procedure is known as passive immunization, or serum therapy, and consists in utilizing in treatment the products of active immunization produced in a living organism other than the patient.

Antipneumococcic Serum is the blood serum of horses that have been highly immunized against the pneumococcus. After selecting a suitable animal, injections are made at pre-

scribed intervals and in increasing doses of killed and attenuated living and finally virulent cultures of pneumococcus. This procedure is continued until a large number of living micro-organisms can be tolerated with but little reaction. The blood of the horse is then tested for antipneumococcic qualities, and if found sufficiently potent a large quantity is withdrawn. The serum is separated from the clot, standardized, and placed in containers for therapeutic use. As with the bacterins, the serum is polyvalent, i. e., in its production numerous varieties of virulent pneumococci are employed.

Standardization.—The immunity unit for antipneumococcic serum, according to Neufeld and Handel, is established by ascertaining the amount of serum (administered subcutaneously) necessary to protect a mouse from a subsequent intraperitoneal injection, four hours later, of 10 to 100 times the lethal dose of living pneumococcic culture. A serum, 0.01 c.c. of which will secure this result, constitutes the standard (normal serum) by which the relative potency of other serum is estimated.

Theoretical Consideration Relating to Curative Serums.—Therapeutic serums may differ widely as to the qualities, potencies and the kinds of antibodies they contain. It is, however, certain that this variation is dependent largely upon the nature of the antigen employed in producing the antibacterial or antibody-forming reaction. To a great degree it is thus

subject to control. For example, if we employ bacteria themselves, while all the various antibodies are to a certain extent present in the serum, the principle antibodies produced are usually opsonins, bactericidins, bacteriolysins, agglutinins, etc.; if only the toxic products of bacterial metabolism are employed the antibodies predominating in the serum are chiefly of the nature of antitoxins, antiaggressins, etc.

It is thus readily seen that in the preparation of a therapeutic serum the chief consideration in the mode of attack of the particular bacteria against which the serum is to be employed. The diphtheria or tetanus bacillus, for example, seldom makes its way beyond the original point of infection in the throat, larynx, nasal passages, etc., the serious manifestations of the disease being due to the powerful toxin which is secreted or manufactured during the process of bacterial metabolism. In producing the antidiphtheritic serum or antitetanic serum, therefore, the toxin alone is employed as the antigen. With its repeated injection into horses they become immune on account of the antitoxin formed in increasing quantities after each injection and which remains present in the blood. The blood serum of the horse then constitutes the "diphtheria or tetanus antitoxin," which has proved so efficacious in combatting these infections. The diphtheria and tetanus bacilli themselves cause little harm and disappear in most cases a short time after the toxin has been neutralized by the antitoxin.

The pneumococcus, on the other hand, forms practically no exotoxins (toxin formed in the process of bacterial growth), but multiplies rapidly and spreads throughout the tissues and even into the general circulation. It is not definitely known whether the pathologic conditions produced are due to the absorption of toxic substances or the destruction of cellular tissues by the bacteria themselves, or to the poisonous action of endotoxins (toxins contained within the bacteria and liberated by the breaking down of the bacterial cells). It is, however, known that in resisting pneumococcic infection the body cells produce opsonins and other antibodies, and that the destruction of the bacteria is brought about by phagocytosis and bacteriolysis. The methods adopted for the preparation of antipneumococcic serum would, therefore, be such as would produce the greatest opsonic and bacteriolytic content; or, in other words, the immunization of the horse with living virulent bacteria. The serum of the immunized horse consequently would have antibacterial properties in contradistinction to the antitoxic serums employed in the treatment of diphtheria and tetanus.

A peculiarity to be taken into consideration when employing therapeutic serums is that their curative power apparently does not follow the law of multiple proportions. That is, a small dose of serum given in a mild infection may have absolutely no therapeutic effect; on the contrary, a large dose of the same lot of serum,

given in a severe infection, will often place the patient on the road to recovery. This perhaps may be explained theoretically as follows: In a mild form of an infectious disease the lack of serious symptoms is probably due, not so much to the small number of bacteria or the small amount of toxins present, but rather to their lack of highly virulent characteristics or poisoning qualities. In such cases the bacteria or toxins present would, however, absorb or combine with the antibacterial or antitoxic bodies injected with the same avidity as in the case of the more virulent infection. Thus a small amount of serum would be quickly neutralized without to an extent affecting the course of the disease. If, however, sufficient serum is given in a mild case to neutralize all of the bacterial products present, as well as to bring about a complete phagocytosis, recovery will ensue. In the same manner a severe infection may be successfully combatted by the injection of sufficient antibodies to neutralize all the toxins and to supply sufficient opsonins for the ingesting of the bacteria by the phagocytes.

Dosage of Antipneumococcic Serum.—The dosage of antipneumococcic serum is from 20 to 60 c.c. every four to six hours for adults—children according to age—governed to a great extent by clinical observation. Probably no two cases are exactly alike in the natural resisting power of the patient, the virulence of the bacteria, or the extent of the infection. As in the administration of diphtheria antitoxin the only

safe rule would be to inject repeated doses of antipneumococcic serum until the crisis is passed or the infection shows a distinct tendency to recovery by lysis, a condition sometimes resulting from the use of the serum as well as in natural recovery. The treatment should, of course, be continued until the patient is out of danger.

Method of Administration.—The serum may be administered subcutaneously or intravenously. The modern trend of opinion, however, in the administration of all serums seems to favor the intravenous method, because large quantities of the specific antibodies may thus be brought immediately into contact with the pathogenic organisms or their toxins. When the serum is injected subcutaneously it is slowly, perhaps incompletely, absorbed into the general circulation, and its action is thus far weaker and more uncertain than when it is introduced directly into the blood stream. When a general septicemia or bacteremia is present, or when an acute infection has reached a serious stage, only the intravenous method is held to be effective. For the same reason in pneumococcus meningitis, intradural injection would seem to be indicated. Experience with antimeningitis serum in cerebrospinal meningitis due to the diplococcus intracellularis meningitis has amply proved that injections of serum subcutaneously or even intravenously are of little avail when the spinal cord and meninges are affected.

Mode of Action.—In pneumonia due to pneumococcus antipneumococcic serum causes a much earlier occurrence of the crisis characterizing the disease. In a case of lobar pneumonia following the well-known classical course there is a gradual increase in severity of the symptoms culminating in a crisis on the seventh day of the disease. If antipneumococcic serum is injected early the crisis tends to occur about the third day and the symptoms are of less severity than in those in which serum therapy has not been employed. It has been observed that many of the usual complications and sequels of pneumonia do not make their appearance in cases in which antipneumococcic serum has been administered.

Clinical Reports.—Beltz (Deut. med. Woch., Jan. 4, 1912) records a series of 25 cases of lobar pneumonia in which injection of antipneumococcic serum was made intravenously within the period preceding the third day of the pneumococcic process, reckoned from the initial chill. The results were as follows: 400 units (Roemer's serum) were given as soon as diagnosis was made. On the following day there was no improvement in the symptoms and a double dose was administered. In several serious cases a third injection was given on the third day, and in a few, further injections were given during the course of the disease. The author compares these 25 with 25 similar cases treated the year previously by the ordinary methods. In the latter series the crisis appear-

ed on the seventh day in nine or 35 per cent., while in those receiving the serum treatment the crisis appeared on the third day in six cases, or 24 per cent. of the total. In those receiving serum treatment the crisis appeared about the seventh day in 15 cases, in four, recovery occurred by lysis, and four died. In two the crisis appeared on the ninth day. Of those who did not receive the serum treatment in all but two cases the crisis occurred on or about the seventh day of the disease; three recovered by lysis and four died. The author does not hesitate, therefore, to recommend the use of antipneumococcic serum in large doses given intravenously in the early stages of pneumonia, especially when a shortening of the duration of the disease is desirable.

Rowland G. Freeman (J. A. M. A., July 13, 1912) reports a series of cases treated with antipneumococcic serum in which alternate cases were used as controls. The patients showed high temperature with good chest signs. There was no evidence of irritation at the site of injection and the serum was rapidly absorbed. The average of the children injected was 20 months, the controls, 11 months. In a number of cases an immediate change in the appearance of the child followed administration of the serum. Patients that appeared septic previous to injection became brighter, of good color, took nourishment better and seemed much improved, although the condition in the lung was unchanged, and in some cases seemed to be

spreading. In some of the cases the serum injected appeared to have no results, but in the majority there seemed to be a better reaction on the part of the child after injection than before.

Matthias Nicholl, Jr. (Ibid) says that after a fairly large experience with antipneumococcal serum with both children and adults, it seems that large doses of the serum should be employed, at least 100 c.c. In a recent attempt to immunize diphtheria patients against secondary pneumonia there was apparently no reduction in the death rate. It was difficult, therefore, to have a great deal of faith in the curative value of serum which had so little protective power against the organism which it was designed to combat. "In view of the fact that good results seem to follow the use of the serum in some cases, it is advisable to use it in prolonged cases which seem to be daily losing ground, but the dosage should be large. I have seen no bad effects from the administration of the serum even though the doses were very large. I prefer to give it intravenously, but 100 c.c. may easily be given subcutaneously.

Geronne (Berl. klin. Woch. Sept. 2, 1912) reports the histories of a series of cases of pneumonia treated by antipneumococcal serum. The fact that the serum should be given early—within the first day or two of the infection, preferably intravenously in large doses—20 to 40 c.c.—is strongly emphasized. Persons so treated developed the crisis before the fifth

day. The serum seemed to have had little influence on a course of disease after the sixth day of infection. In three cases in children the author clearly demonstrated that the effect was not due merely to the foreign serum but to the antipneumococcic substances it contained. He injected normal horse serum and sheep serum and also antistreptococcic serum without any demonstrable effect. Serums should be highly polyvalent that is, include all strains of pneumococci obtainable.

CHAPTER XI.

Bacterins.

(Continued)

Pyocyano Bacterin.—Relative to the pyocyano-bacterin, the following is quoted from Working Bulletin No. 1, Third Edition, June, 1911:

The successful treatment of a case of pyemia due to this organism (*Bacillus pyocyaneus*) is recorded by Groves (Br. Med. Jour., May 15, 1909, p. 1169). There was a history of hip-joint trouble dating back nine months. An operation was performed, and the head of the femur and the socket found to be eroded. The day after the temperature rose to 103° F. and remained there for five days when it began to fluctuate three or four degrees, rising as high as 104° F. Delirium, emaciation, multiple abscesses followed. Six weeks after operation the bacillus pyocyaneus was recovered in pure culture from the sanious discharge. A vaccine was made, and 40,000,000 given, without any appreciable result. Eight days later, when the temperature was 101.5° F., 60,000,000 were given. Within two days the temperature fell to normal and remained there. At, intervals of ten, fifteen

twenty-three and fifteen days, respectively, injections of 100,000,000 were given. From the date of the second injection the whole condition rapidly improved; quiet sleep was secured, and food was well taken; weight was put on rapidly and all the abscesses and sinuses healed, except one quite small superficial one. The surgeon concluded that a more striking example of the potency of vaccine therapy could hardly be imagined. The bacillus pyocyaneus is frequently the offending organism in suppurative middle ear disease.

Staphylo-Bacterin.—With the staphylo-bacterin, as with all other vaccines of this character, that it is the indicated agent must be known, and this is determined through the use of the opsonic index. If the infection is not due to the staphylococcus, the staphylo-bacterin will prove ineffective, whereas, in the face of a contrary clinical diagnosis, as when the Neisser-bacterin fails, the staphylo-bacterin may give good results. It is imperative that proper diagnosis be made, either clinically, through the use of the laboratory determination of the bacteria present, or by use of the opsonic index.

The staphylo-bacteria is frequently indicated in the treatment of acne, carbuncle, eczema, furunculosis, sepsis and gonorrhea, and is employed as an immunizing agent to prevent infection.

If the flow of blood is impeded through the associated "brawny swelling," the addition to the treatment of citric acid, or sodium citrate,

a dram three times a day, with local applications of sodium citrate to the infected area, will serve to overcome this obstacle and allow of the blood reaching the infected focus.

Relative to the application of staphylo-bacterin, and other data regarding it, the following is obtained from Working Bulletin No. 3, Second Edition, June, 1910:

Dosage.—The proper dosage of bacterins is largely dependent on the nature of the case. The more chronic the case, the larger doses will ordinarily be required. The initial dose may vary from 25,000,000 to 250,000,000. It is generally wise to start with a small dose and increase it according to the indications, basing the increase on the following points: After a proper dose there is a sense of well-being which lasts an hour or two, followed by a sense of depression with increase of the local phenomena, the "negative phase". This should last a day or two and be followed by improvement, which should last from four to twenty days, the "positive phase". If there is no negative phase, the dose is too small; if the negative phase is very severe or lasts more than three days, the dose is too large. The dose should not be increased as long as a negative phase follows each injection, even although the bacterin has been used for a long time. Many clinicians make a primary injection of 125,000,000 and if no negative phase occurs at the end of three to five days, they administer 250,000,000, to be followed, if there is no negative phase, at another interval

of three to five days by 500,000,000. Where a negative phase occurs, the dose previously used should be repeated. If the negative phase is severe, or lasts over three days, it is advisable to reduce the dose. Smaller doses should be used in acute and extensive infections.

The site of injection is not of very great importance; but, when possible, it should be at a point from which the lymph drains through or past the local lesion. It has been suggested that bacterins be administered by the mouth, but not enough work has been done to establish their efficacy or dosage when administered in this way.

Interval Between Doses.—The proper interval between doses must be decided for each case. In acute cases it will vary from two days to a week; in more chronic cases ten days to three weeks. If the opsonic index is taken, the second dose should be administered as soon as this falls to normal. If this is not used as an indication, the second dose should be given as the positive phase begins to decline, as shown by cessation of clinical improvement.

Clinical Reports.

Acne.—The results in acne have been very encouraging. The following papers may be referred to as typical:

Dr. Ramsbolton (Lancet, 1907, Jan. 5) read a paper before the Manchester Pathological Society in which he spoke of the use of staphylococcus bacterin in the treatment of furuncu-

losis and severe forms of acne. Mild cases of acne do not seem to yield so rapidly to the treatment. In the severe forms the opsonic index was always found to be low to staphylococcus; in the milder forms this was not the case.

Dr. Alex C. Soper Jr. (Chicago Med. Rec. 1907, 105; 1909, Feb.) reports twenty cases, most of them of furunculosis in infancy. A careful study of stock bacterins in comparison with autogenous bacterin shows little difference. Of five cases treated with autogenous bacterin all were cured and of fifteen treated with stock bacterin twelve were cured. He reports in outline five of the cases, all of bad furunculosis, which were cured by an average of a little more than two injections.

French (Br. Med. Jour. 1907, i, 256) reports the use of staphylococcus bacterins in the treatment of acne. He finds that it is of the greatest service and even in the worst cases brings about marked improvement in the complexion. After six doses at similar intervals, the eruptions can be kept under with very little trouble, but it is best to continue the injections. In cases of long standing, in which there is induration of the skin, Eberts and Hill (Am. Jour. Med. Sci. 1907, ii, 35) recommended the use of hot water applications for a period of twenty minutes daily, in connection with the injection of bacterin in order to draw the freshly opsonized blood to the focus of infection.

Inflammatory Skin Affections.—That the

treatment is also effective in boils, carbuncles and other suppurative and inflammatory skin conditions, the following reports will show :

Geo. W. Ross (J. A. M. A., 1907, ii, 1245) reports a series of cases treated by staphylococcus bacterin. He has treated boils, carbuncles, acne and septic wounds. In nine cases out of eleven the pain was relieved within forty-eight hours. Cases are likely to relapse, and for this reason injections should be continued after apparent cure. A large carbuncle was cured by one injection, which relieved all pain and tenderness within forty-eight hours. The results in sycosis have been very promising.

Dr. Harlin, Chicago, reports good results in cases of sycosis as well as in those of acne.

Wechselman and Michaelis (Deut. med. Woch., 1909, xxv, 1309) report that treatment of staphylococcus diseases of the skin with staphylococcus bacterins. They believe that it is a remarkably effective treatment. Only in exceptional cases is it necessary to prepare an autogenous bacterin, a polyvalent stock bacterin being ordinarily effective. Five cases reported in detail.

Boehme (Deut. Arch. fur klin. Med., 1909, xvi, Heft. 1) reports a series of cases treated with staphylococcus bacterins, and states that clinical improvement goes hand in hand with a rise of the opesonic index.

Ohlmacher (J. A. M. A., 1907, i, 571; 1908, ii, 571; Am. Jour. Sur. 1907, Dec.) reports a series of cases treated by bacterins, among which are

the following cases of staphylococcus infection: He has treated two severe cases of acne vulgaris of one and two years standing with autogenous bacterin. In one case, after eight injections, nodules ceased to appear and seborrhea had given place to a normal skin. In the other case, six injections have cured a most repulsive indurated acne of the face. A case of impetigo was also treated with autogenous bacterins. The first injection brought the disease to a standstill and the second injection affected a cure. In a case of recurrent impetigo of four-teen months duration, two injections affected a cure. A two-year-old girl, in whom boils resulting from infected mosquito bites had lasted six weeks, was cured by one injection. Two similar cases were cured by three injections each. Dr. Ohlmacher also reports a case in which furunculosis of the arm-pit was followed by sup-puration of the axillary glands and "it was clear that a total extirpation of the affected area would be necessary." The first dose of stock staphylococcus bacterin stopped the inflammation, and a second dose resulted in the cure of the infected glands, with the exception of three, which had already softened and which healed promptly after evacuation. A very interesting case was that of a woman who presented a dermatosis which covered a large part of the body and which was diagnosed as psoriasis. The condition had lasted eighteen months and the patient was confined to her room. A lesion was excised and planted on glycerine

agar. A growth of *staphylococcus pyogenes aureus* resulted, from which a bacterin was prepared and injected every seven days, cure resulting after five injections.

Dr. Mark Richardson (Bost. Med. and Surg. Jour., 1908, clviii, 37) reports six cases of pustular acne which have been treated with *staphylococcus bacterin* with very marked improvement. In two cases they were autogenous, in four they were not. The cases seemed to do equally well. He believes that greater success would be obtained if injections were combined with a bacterin from the bacilli acne.

In a letter to the Lancet Dr. Geo. Wm. Davis (Lancet, 1909, ii, 958) reports a case of troublesome eczema of the beard which had resisted all other treatment and spread to the external ear. He finally began the use of stock *staphylococcus bacterin*, giving injections alternately in the right and left forearms. He began with 100,000,000 and increased to 500,000,000. Each injection caused a slight local reaction. After five injections the eczema of the beard had entirely cleared up and the trouble was confined to one ear. After the fifth injection (500,000,000) a very acute pain, lasting two days, was experienced, the forearm became swollen and the temperature commenced to rise. For two nights the patient could not sleep. The injection, however, was followed by a complete recovery from the last remains of the eruption. He believes from this experience that an interval of one week between inoculations is unne-

cessarily long, and suggests that between doses of 100,000,000 he would first allow an interval of four days, and then one of three days, then an interval of two days. Between injections of 100,000,000 and 250,000,000 he would allow four days, if possible. He usually uses three injections of 250,000,000 with intervals of seven, six and five days, then an interval of ten days, followed by an injection of 500,000,000 and, if necessary, continues inoculations of 500,000,000 with intervals of ten days. He believes that bacterin treatment should be used in all cases of eczema which resist other treatment.

In a later letter (*Lancet*, 1909, ii, 1382) Davis reports a case of eczema in a boy of sixteen, which was treated with staphylococcus vaccine. The entire face and anterior part of the trunk and thighs and legs were covered with the eruptions, as were the flexures of the elbows, the front of the forearms and the palmer aspects of the hands and fingers. The injections of the vaccine were all made in to the arms. Each injection was followed by local induration, and the next injection was given as soon as this induration disappeared. There was very little pain and no constitutional disturbance following the injection. The doses were from 100,000,000 to 1,000,000,000. Nine injections were given in the course of six weeks, during which time the eruptions cleared up entirely except for a few scattered spots.

Dr. R. T. Thorne (*Br. Med. Jour.* 1907, Feb. 23) reports a case of furunculosis of three years

duration, in which he tried every ordinary method of treatment without effect. He finally used a staphylococcus bacterin, and after six injections the skin cleared up entirely and the patient has remained in perfect health.

Dr. George Wolfshon (Berlin, *klin. Woch.* 1909, xlv, 1017) reports a series of cases which he has treated with staphylococcus bacterins. He prefers the autogenous when these can be obtained, but recently he has secured very good results from the use of stock bacterins. He has abandoned the use of the opsonic index. He gives the inoculations every six to ten days, and believes that one must be careful in increasing the original dose. He has never given more than 250,000,000 staphylococci. He reports in detail five cases of furunculosis, all of which were treated with good results. A case of obstinate acne of the face and back, in which other treatment had been given without result, was cured by five injections. Three cases of paronychia were cured by from two to four injections each. A case of large carbuncle on the back of the neck was entirely cured by four injections. He reports one case of osteomyelitis of the tibia in which bacterin treatment was used without avail. A case of puerperal mastitis was treated with good results.

Maute (*Wein. klin. Woch.* 1909, xxii, 1083; *Presse Med.* 1909, 334) states that he has obtained good results in the treatment of furunculosis by the use of staphylococcus bacterins. He believes that this treatment not only has-

tens the cure of the lesions, but is particularly effective in preventing the occurrence of new ones.

Sellei (Wein. klin. Woch. 1909, xxii, 1485) reports 15 cases of furunculosis, 14 cases of sycosis, and 12 cases of acne, treated with bacterins. The results in the cases of furunculosis and sycosis were almost always strikingly good. The cases of acne were much more stubborn and showed a greater tendency to recurrence, although the benefit obtained from the injections was usually noteworthy. The author believes that if the acne bacillus were used in connection with the staphylococcus the results would be just as striking as those obtained in the treatment of the other diseases. In sycosis it is necessary to use local treatment in connection with the bacterin treatment.

Stubell (Muen. Med. Woch. 1909, lvi, 1152) has treated furunculosis, acne, sycosis, eczema, etc., with remarkably good results with staphylococcus bacterins. In discussing this article, Galewski reports that he has had good results in the treatment of acne.

Dr. Robert M. Merrick (Ann. of Gyn. and Ped. 1908 210) has found the staphylo-bacterin useful in the treatment of "suppurative skin conditions complicating marasmus or malnutrition, such as furunculosis, pemphigus neonatorum, pustular eczema and decubitus sores, which may vary from a slight abrasion to a gangrenous wound." The good results following staphylococcus vaccine in these conditions has led to its routine

use at St. Mary's Infant Asylum. The vaccine was used without determining the opsonic index, and the amount used and the number of injections were governed solely by the clinical symptoms. He reports fifteen cases, most of them pustular eruptions, eczemas, boils or furunculosis. Only one case showed any bad results following injection. In this case the second injection was followed by marked depression and vomiting, which lasted a few hours. In twelve of these cases the treatment was followed by marked improvement. The improvement was not always permanent, and the author concludes that the numerous instances of re-infection suggests the continued use of vaccine after the lesions have cleared up. The site of the injection seems to be entirely immaterial, and the injection is not usually followed by any local reaction. He suggests that the vaccine might be given by mouth instead of by injection.

Theo. C. Beebe and Leon Medalia (Bost. Med. and Surg. Jour. 1908, clviii, 85) state that small doses of bacterin, so long as they produce a negative phase, are of more benefit than increasing doses. When the injection no longer gives a negative phase, or the patient's condition is at a standstill, an occasional large dose may be used for its stimulating effect. In cases of mixed infection inoculations of one bacterin will raise the opsonic index not only to the same bacteria, but occasionally to others. In cases of mixed infection the opsonic index

may be found low to several of the bacterin. In such cases we secure cultures of each organism if possible, and inject bacterins from each separately, continuing to use that organism which brings about the greatest change in the index. When cultures show a growth of staphylococcus, a stock bacterin, made from five or six virulent strains, often gives better results than an autogenous bacterin. The following cases of staphylococcus infection are reported. Two cases of furunculosis which had lasted several months each, and had shown a very large number of boils, were cured by respectively five and eight injections. In one of these cases it was necessary to use the bacterin in rapidly increasing doses, as no negative phase occurred with small doses. Another case of furunculosis which had lasted three months was cured by five injections, but two months later the boils began to appear, and two more injections were required to bring about permanent cure. In one case of acne there was marked edema of the whole forearm after each injection; the patient was subject to attacks of angio-neurotic edema and the condition was not inflammatory. In addition, six cases of mixed infection are reported in which staphylococcus bacterin was used in connection with others. Three of these were cases of mixed staphylococcus and colon infections, two of staphylococcus and pneumococcus, and another mixed infection in tuberculosis. In each case the corresponding bacterins were used, and the

result of the treatment in each case was favorable. It was found in these cases that the reaction in the different patients to the same dose was even less regular than in the case of pure infection.

Hartwell and Less (Bost. Med. and Surg. Jour. 1907, Oct. 17) have treated one hundred cases of staphylococcus infection with stock bacterin. The initial dose was 300,000,000 organisms and the succeeding doses 600,000,000. The injections were given at regular intervals of four days until the lesions were cleared up. The authors regard this treatment as the most effective for boils and carbuncles.

Nathaniel Potter (J. A. M. A. 1907, ii, 1815) points out the variations in the opsonic index caused by various affections, and in conclusion reports a few cases. Three cases of chronic facial acne improved rapidly after the use of a stock staphylococcus bacterin. A carbuncle of the neck was cured by two injections.

Dr. Isadore L. Hill (Charlotte Med. Jour. 1909, 231), Dr. Wm. H. Park (Bost. Med. and Surg. 1907, ii, 49), Dr. Arthur Whitfield (Practitioner, 1908, 697) Dr. A. Butler Harris (Practitioner, 1908, 657) Dr. J. H. Wells (Practitioner, 1908, 655), and many others also report good results from the use of staphylo-bacterins in the treatment of acne, boils and similar pustular skin conditions.

Septic Infections—The following reports are typical of those concerning septic infections:

Gildersleeve and Carpenter (Arch. of Ped.

1907, 689) report a case of a boy nine years old, who had numerous abscesses in different parts of the body, followed by gangrene of the toes and bed-sores. An autogenous bacterin was prepared, and three injections resulted in the healing of all abscesses and almost a complete cure.

Ross (J. A. M. A. 1907, ii. 1245) mentions, but does not report in detail, a case of a septic infection of the hand and one of orbital infection, which were cured by the use of staphylococcus bacterin.

Christie (J. A. M. A. 1910, i, 705) states that he has had remarkably good results in the treatment of acute and chronic otitis media with injections of staphylococcus bacterin. He has treated 18 cases, 16 of which were permanently cured. In the other two cases three was dead bone, and though both patients improved under the use of the bacterin, they always relapsed when the treatment was discontinued. The first dose should be 125,000,000 increased to 250,000,000. The author concludes that "no one can treat by inoculation one of these obstinate cases of otitis media which refuses entirely, or only after prolonged treatment, to yield to local means, without reaching the conclusion that bacterial inoculation is a powerful agent for the cure of this disease.

Rooker (J. A. M. A. 1910, i, 126) reports two cases of furunculosis and one of prostatitis, which were cured by injections of stock staphylococcic bacterin given in doses of from

100,000,000 to 400,000,000. The case of prostatitis was cured in six weeks, the injections being given every three days. This patient was also affected with pulmonary tuberculosis, having a severe cough, and having had three hemorrhages. Within a week after the bacterin treatment was begun the cough was markedly improved and the patient's weight had increased eight pounds. This was, no doubt, due to the effect on a mixed staphylococcic infection. The cases of furunculosis were in children aged eight months and eighteen years. The first case was treated with doses of 5,000,000 repeated twice at intervals of seven days. The second case was treated with three injections of 100,000,000, 200,000,000, and 300,000,000, respectively. No more boils appeared in either case after the bacterin treatment was begun.

MacGowan (Cal. State. Jour. of Med. 1910, viii, 82) reports two cases of chronic cystitis treated with staphylo-bacterin. The first case showed a tendency to a septic condition, which suggested the use of bacterins. After four injections, at intervals of two days, the general condition cleared up, and there was no return of the septic trouble. The other case was very similar, the washings from the filtrate showing pure culture of staphylococcus aureus. The corresponding bacterin was therefore used in doses of 80,000,000. After two of these doses the temperature had fallen from 102.6° to nor-

mal, and the septic condition which had previously existed was entirely relieved.

Ohlmacher (J. A. M. A. 1907, i, 571; 1908, ii, 571; Am. Jour. Surg. 1907, Dec.) reports a case of pyelitis and several cases of middle ear infection cured by the use of bacterins. He believes that in tuberculosis there is generally a mixed infection and that it is, therefore, wise to combine the use of tuberculin with a bacterin of staphylococcus or other complicating forms. In suppurative syphilitic lesions it is also wise to combine specific treatment with the use of bacterins. Ohlmacher believes that the proper interval between injections is about a week. Another interesting case, reported by Ohlmacher, was that of palmer abscess, in which anti-streptococcic serum had been used without effect. An injection of stock staphylococcus bacterin prevented further extension of the inflammation and three injections of an autogenous bacterin completed the cure, a small abscess being opened.

Stubell (Deut. med. Woch. 1909, xxxv, 242) in an article on bacterin therapy, reports cases, most of which were skin abscesses, treated with staphylococcus bacterins, in which the results were very encouraging. In a case of puerperal sepsis, due to staphylococcus, the use of staphylo-bacterin did not save life, although improvement was noted after each injection.

Dr. Lee (Bost. Med. and Surg. Jour. 1908, Jan. 2) believes that the opsonic index is of less value as an indication of the interval be-

tween doses than the clinical symptoms. It may be necessary to inoculate an extremely sick patient every twenty-four hours, while during convalescence every five days is sufficient. It is not enough to know that the infecting organism is staphylococcus, the variety must be known. A case reported of septic inflammation of the finger, due to staphylococcus citreus, in which an aureus bacterin was without benefit, but prompt cure resulted from the use of the citreus bacterin. In a case of cervical abscess due to staphylococcus albus, inoculation with aureus was without benefit, but after two inoculations with albus the patient was able to return to work. Dr. Lee believes that if we cannot determine the exact species responsible for the infection, the use of vaccines is inadvisable.

Dr. Gilman Thompson (Asso. Am. Phys. 1909, May 11) reports a series of cases treated with bacterins, among which are the following: A boy, aged sixteen, was taken ill, with ulcerative endocarditis, two weeks before being brought to the hospital. Ten injections were given in the course of sixteen days. After this time the temperature remained normal and the patient was entirely cured of septicemia. The second case was an infection of the forearm, following a burn on the hand. Septic pneumonia followed, and there was suppuration of the wrist, requiring incision. On the fifteenth day arthritis of the right knee-joint developed, on the nineteenth day pyonephrosis was dis-

covered, and on the twenty-seventh day a rapidly spreading abscess formed over the upper side of the chest wall and shoulder. The next day bacterin treatment was begun, and such prompt improvement followed that the surgeons who had previously refused to operate, because they believed the patient could not live more than a few hours, opened the abscess on the shoulder and removed twelve ounces of pus. Four subcutaneous inoculations were given at weekly intervals, three of 100,000,000 and one of 200,000,000. Immediately after the first inoculation the temperature, which had averaged 103° , fell to 101° , and the patient showed great improvement. Subsequent slight elevations were controlled by further injections, until, after two months of fever and one month from the first inoculation, the temperature remained normal and recovery was complete, the patient leaving the hospital with but moderate stiffness of the knee-joint.

Floyd and Worthington (Bost. Med. and Surg. Jour. 1908, Jan. 2) report a case of facial carbuncle followed by angina and parotitis, successfully treated by staphylococcus bacterin, combined with administration of citric acid. A girl seventeen years old had a pimple on the right cheek, which was followed by inflammation of the skin and carbuncle of the upper lip. She was unable to open her mouth and was somewhat delirious. Fifty millions stock staphylococcus was administered. Two days later a culture showed staphylococcus aureus, from

which a bacterin was prepared and 25,000,000 inoculated. Three days later definite improvement was noted and another injection of 25,000,000 was given. The next day the blood was found to clot almost immediately upon being drawn, and for this reason, dram doses of citric acid were given for four doses. This resulted in a very marked improvement. The citric acid and bacterin treatments were continued for four days, when the parotid gland became enlarged and painful. A further injection of 50,000,000 staphylococci caused a reduction of the swelling and a gradual clearing up of the condition. The physicians believe that life was saved by the use of the bacterin.

Dr. Hartwell (Mass. Gen. Hosp. Rep. xi, 1) reports from the Massachusetts General Hospital, good results in the treatment of localized staphylococcus infections, from the use of bacterins. He uses an original dose of 300,000,000 and continues with doses of 600,000,000 until cure occurs. In obstinate cases recurrence should be prevented by three or four injections given at intervals of a week after apparent cure.

Dr. Helen Putnam (Bost. Med. and Surg. Jour. 1908, clviii, 15) reports a visit to Dr. Almoth E. Wright's clinic. She says that Dr. Wright believes that in practically every local infection there is an obstruction of the blood-current, preventing sufficiently free access to the pathogenic bacteria. He therefore inoculates at a point where the newly formed opson-

ins will drain through the diseased tissues on their way to the general circulation. For this reason he most frequently injects in the back of the shoulder when the trouble is in the face and head. A cumulative result cannot be obtained in the use of vaccines either by giving a dose before the effect of the previous one has passed off, or by giving progressively increasing doses, or by giving a larger dose because a smaller one has done well for some time. After the correct dose there is usually within an hour a wave of improvement, sometimes evident in the lesions, sometimes in the feelings of the patient. This improvement is brief, and during the following twenty-four hours or so a negative phase always occurs, with feelings of depression. After this the condition again improves, until by the third or fourth day the greatest improvement is reached, which is gradually receded from during the week. At the end of this period is the time to give a new dose. Dr. Putnam reports the following case of staphylococcus infection from Dr. Wright's clinic: A woman had run a splinter in her finger several weeks before and this was followed by many pustules on the back of the forearm. An injection of autogenous staphylococcus bacterin was administered, but the patient showed little improvement. A bandage was then wound around the arm and the resulting congestion forced more lymph into the inflamed areas and also forced bacteria into the

blood current, producing anto-inoculation. This resulted in improvement.

As a Preventive of Infection—Pray (Edinburgh Med. Jour. 1909) uses staphylococcus bacterins as a preventive of infection in surgical work. He injects 500,000,000 staphylococcus and 150,000,000 to 250,000,000 streptococcus about one week before the operation. He believes that in this way, in some cases, he has prevented the occurrence of post-operative pneumonia.

Tuffer (Presse Med. 1909, p. 689) speaks of attempts which have been made to prevent infection after operations. He states that he has had good results from the injection of killed cultures of staphylococci prepared according to Wright's method.

Mixed Infection—Two abstracts will serve to show the advantages of using staphylo-bacterin in mixed infections. Dr. G. A. Grace-Calvert (Med. Rec. 1907, 327) advises the use of staphylococcus vaccine in association with tuberculin treatment in cases of mixed infection in phthisis.

W. M. Robertson (J. A. M. A. 1909, ii, 797) reports a series of cases of genito-urinary infections in which staphylococcus bacterin was used. He has obtained the best results in cases of chronic urethral discharge following gonorrhea, but in which no gonococci were found. In cases due to staphylococcus he considers it almost specific. He has used it in twenty cases of prostatitis and cystitis with a history of

gonorrheal inflammation dating back from a few weeks to many years, and has not met with a case in which the subjective symptoms were not relieved by the third injection. If the injections are given every five to seven days with other appropriate treatment, the case goes on to complete recovery with surprising rapidity. The injections are probably of value in cases of scanty purulent discharge from the prostate, even when this is of long standing. In cases of cystitis following instrumentation or spinal lesions, the results have been gratifying, especially when the infection was due to staphylococcus. He reports six cases of gonorrhea and prostatitis, and a case of very marked improvement in locomotor ataxia following injections for cystitis, but he is very conservative about ascribing the good results in this case to the use of bacterin. He also reports a case of tuberculosis of the kidney which showed marked improvement under the use of staphylococcus bacterin and tuberculin.

Robertson gives the injections every other day until after the third injection, then every five to seven days as long as they seem to be indicated. Only staphylococcus albus bacterin was used and always in doses of 400,000,000. He has given several hundred injections and has never seen an abscess follow one, nor had a complaint from pain or other bad effect.

CHAPTER XII.

Bacterins.

(Continued)

Strepto-Bacterin. Anti-Streptococcic Serum

—As both the anti-streptococcic serum and strepto-bacterin are employed for treatment of like conditions they will, because of this fact, be considered under a single discussion.

The serum is employed in the treatment of pyemia, puerperal sepsis, scarlet fever, erysipelas and mixed infections, while the bacterin is indicated in local infections, erysipelas, puerperal sepsis, mixed infections, septicemia and as a preventative of scarlet fever and peritonitis.

As to the clinical applications of anti-streptococcic serum, the following data is cited:

PYEMIA.

Yervant (Reforma Medica, Apr. 27, 1908) reports a case of pyemia following middle ear disease, which was treated with anti-streptococcic serum. The mastoid was opened, but without benefit. An injection of anti-streptococcic serum reduced the temperature to normal in a few hours. Several injections were given, and although the patient was threatened

with arthritis the recovery was without further trouble. In one patient, seventy-five years old, who was not operated upon, the temperature had risen to 106.7° , but after an injection of anti-streptococcic serum it fell to normal. When the serum treatment was suspended the patient rapidly grew worse, and finally died.

Peabody (Med. Rec. 1908, i, p. 423) reports a case of cerebrospinal meningitis of streptococcic origin apparently cured by subdural injection of anti-streptococcic serum. Ten c.c. of the serum were given for the first dose, and repeated the second day, without benefit. The third day 10 c.c. of cerebrospinal fluid was withdrawn and replaced by 10 c.c. of anti-streptococcic serum. This was repeated at intervals of twenty-four hours, until four doses had been given. Two more doses were given at intervals of forty-eight hours. After the second injection the spinal fluid was always found sterile. The temperature fell to normal, showing a slight rise each day for six days. Kernig's sign was present ten days after the other symptoms had disappeared.

PUERPERAL SEPSIS.

Bumm (Berlin. klin. Woch. Oct. 31, 1908) states that for the last ten years he has used an anti-streptococcic serum in the treatment of puerperal fever. In five cases of general septic peritonitis, as well as in four cases of post-operative peritonitis, the treatment was unsuccessful. In three cases of septicemia from

streptococcic endometritis two ended fatally and one recovered. In two cases with endocarditis the serum was without benefit. In 53 cases the serum treatment was begun early, while there was only septic endometritis. In each case streptococci had been detected microscopically. Thirty-two of these cases were very severe, and six of the patients died, one of peritonitis and five of pyemia. In 17 of them streptococci were found in the blood, and the author feels that 26 recoveries is a very good result. He finds that the temperature nearly always falls immediately after the injection, even in cases which end fatally, and there is distinct phagocytosis about twelve hours later. The appearance of leucocytes containing streptococci is direct evidence of the beneficial action of the serum. Bumm doubts whether the intravenous injection of the serum is entirely safe.

Rothrock (Minn. Med. Jour. 1909, p. 632) reports the use of antistreptococcic serum in puerperal sepsis. The streptococcus pyogenes probably represents only one species, in spite of the great variability of its virulence. However, serum prepared from an animal immunized to several strains of organisms is more effective than that in whose preparation only one strain is used. The serum finds its greatest use in the early stages of infection and if used early it is certainly a very valuable agent.

The author treated six cases of streptococcic puerperal infection with the serum, and in some

cases the results were nothing short of brilliant, this being essentially true of cases in which the serum was administered within a few hours of the initial chill. All six of these patients recovered, four of them promptly. The temperature falls a few hours after the first injection, but the fall is seldom pronounced until after the second or third doses have been given. The usual dose was 10 c.c. every twelve hours. As the serum is harmless, it would seem good practice to administer at least one dose in every case of puerperal sepsis with sudden onset, as the greatest benefit is seen when the treatment is begun early. If the treatment is not begun until forty-eight hours after the initial chill it is doubtful whether any benefit will be obtained.

Leary (*Intercol. Med. Jour. Austral.* Nov. 20, 1905) reports five cases of puerperal sepsis which were successfully treated with anti-streptococcic serum. He gives 10 c.c. as the first dose, and repeats this two or three times within the first twenty-four hours. If the patient does not react properly the dose may be increased to 20 c.c. Unless the patient is seen early there should be no local treatment, as this does harm if the infection has spread above the uterus.

Heynemann and Barth (*Arch. fur. Gyn.* 1909, lxxxviii, p. 1) report the use of anti-streptococcic serum in puerperal sepsis. In vitro the serum did not possess as marked opsonic power as the serum of normal puerperal patients. The

results were not improved by the addition of either normal human or horse serum or by the use of horse leucocytes. The activity of the antistreptococcic sera is, however, not dependent upon their contents in substances which induce phagocytosis. Experiments on animals give the impression that the ordinary therapeutic dose is too small.

SCARLET FEVER.

Young (Practitioner, Jan. 1909) speaks of the use of polyvalent anti-streptococcic serum in 75 cases of scarlet fever. In cases previously treated without serum 22.6 per cent. showed marked inflammation of the tonsils. In the cases treated with the serum there was only 2.6 per cent. inflammation. There were no cases of severe angina, and no suppurative cases. In one case there was gangrenous angina at the time the serum treatment was commenced, and this was favorably influenced. In cases treated without serum otitis occurred in 20 per cent.; in those treated with serum in only 8 per cent. The occurrence of nephritis was not influenced. The acute stages of the disease appeared to pass over more rapidly in cases treated with the serum. As routine treatment in mild cases, 10 c.c. daily was used. In septic cases 20 to 40 c.c. were given two or three times a day.

In 21 cases of diphtheria the anti-streptococcic serum was used in combination with diph-

theria serum, and the results seemed to be advantageous.

Young (Br. Med. Jour. 1907, i, 745) reports a case of cervical abscess following scarlet fever, treated with anti-streptococcic serum. The abscess had been opened, and at the time the serum treatment was begun had been discharging for thirty-eight days; 10 c.c. of the serum was administered, followed by the same amount the second day. Two days later 20 c.c. were given. The following day there were only a few drops of pus on the dressings, and those were the last seen, and in four days the wound was absolutely united. A week later there was earache and mastoid tenderness and as it was feared that mastoiditis might follow, an injection of 10 c.c. was given, followed the next day by 10 c.c. The following day the temperature was normal and the ear discharge was lessened. Five days later the discharge had ceased entirely and the child made an uneventful recovery. It appears that in this case the anti-streptococcic serum put an end to a long standing cervical abscess in a manner very short of wonderful, while later on it prevented a septic development in the mastoid cells. In both cases without creating any ill effects.

Christison (St. Paul Med. Jour. 1906, Dec.) reports the use of anti-streptococcic serum in 42 cases of scarlet fever all of which were of severe character, and in 31 of which streptococci were found. There were four deaths. The treatment appeared to be beneficial.

Moltschanoff (*Jarbuch fur Kind.* 1907, lxvi, p. 503), during extensive experiments in Russia, found that the mortality in severe cases of scarlet fever was reduced from 47.6 to 16.1 per cent. Large amounts of the serum were required. The temperature always fell after the use of the serum, and sometimes the pulse and respiration showed marked improvement, but this was not always the case. The duration of the fever did not seem to be influenced, nor were the throat lesions affected. The author states that unless the serum treatment is begun before the fourth day of the disease, it should not be used.

Blacher (*St. Petersburger Med. Woch.* 1909, No. 20) speaks of the treatment of scarlet fever with anti-streptococcic serum. He states that beneficial action is almost constantly shown by a striking improvement in the general condition of the patient, a decided fall in the temperature, and an improvement in the condition of the throat, but these advantages are obtained only if the serum is used early in the disease.

Compston (*Br. Med. Jour.* 1908, i, May 30) states that he has used the serum treatment in septic and severe cases of scarlet fever, with 11 deaths in 37 cases. The previous mortality was very much higher. In very severe cases intravenous injections seem to give more prompt relief than subcutaneous injections. Within forty-eight hours of the injection the temperature began to fall and in another forty-eight

hours became normal. All involvement of the throat cleared up in most cases. The serum should be used early in the disease, in doses of not less than 50 c.c. This will produce a marked improvement in septic cases.

Zuppinger (Wein. Iklin. Woch. 1905, No. 44) states that he has employed anti-streptococcic serum in severe cases of scarlet fever. Of 139 cases which he has treated in the last two years 28 were considered severe enough to require the serum treatment. Of these 23 recovered, this being a much better result than was anticipated. It is of great importance to give the serum as early in the disease as possible, preferably in the course of the first three days. The serum was found to be the most valuable in cases of well marked pharyngeal involvement. The injection was usually followed by a fall in temperature of from one to four degrees. From 100 to 300 c.c. of the serum were given, according to the severity of the case. In severe cases with simultaneous diphtheria the anti-streptococcic serum was combined with anti-diphtheritic serum. The author concludes that anti-streptococcic serum is the only remedy in the most severe cases.

Robinson (Pediatrics, 1908, 384) reports five cases of scarlatina treated with anti-streptococcic serum, all of whom recovered. He concludes that the temperature and pulse fall in about thirty-six hours after the injection. Serious cases are made mild. Complications are

prevented or diminished. Convalescence is favored.

ERYSIPELAS.

Ayer (Med. Rec. Mar. 4 and Aug. 6, 1905) reports the results of 48 cases of erysipelas with anti-streptococcic serum. He finds that the average duration of the disease was seven days, as compared to an average of nine and a half days in cases treated by other methods. There is a general improvement of the condition of the patient, and the febrile albuminuria which is present in a large proportion of the cases is always diminished. The efficacy of the treatment is in direct ratio to the length of time which has elapsed between the onset of the disease and the first injection.

Orton (Med. Age. 1906, p. 92) reports a bad case of facial erysipelas treated with anti-streptococcic serum. On two successive days 20 c.c. were injected into the back, with no benefit. The next 20 c.c. were injected in four places immediately in advance of the line of demarcation, and this was repeated in the afternoon. The following morning the patient's temperature was normal and the swelling of the face had entirely disappeared. The author believes that in the treatment of erysipelas the serum should be injected in large quantities immediately in advance of the line of demarcation.

Forneca (Bul. Gen. de Ther. Sept. 8, 1905) uses serum from patients suffering from ery-

sipelas, in doses from 10 to 90 c.c. hypodermically. In nine cases which were treated by this method the headache and delirium disappeared, the appetite improved, and the temperature fell after the injections. When albuminuria was present it disappeared. He found that the serum does not possess any bactericidal power on the streptococci, although it may diminish their virulence. It exhibits an agglutinating power towards streptococci which is more marked in regard to organisms from erysipelas than from other lesions. Normal serum does not exercise any influence upon the course of erysipelas, but blood serum from the patient, heated to a temperature of 55 degrees C, and then re-injected, has the same effect as the serum of convalescents.

Bouttiau (An. de la So. Med-Chir. de liege, June, 1906) reports results in the serum treatment of erysipelas in children. He considers the injection of anti-streptococcic serum the only rational treatment, and opposes the administration of internal remedies, with the exception of an anodyne or a sedative. He objects to the use of any ointment and simply dusts the surface with starch. The injections have had no bad effects, and they certainly reduce the fever and shorten the disease.

MIXED INFECTION.

Roussel (N. O. Med. and Surg. Jour. 1908, lvi, 198) reports 12 cases of streptococcic infection treated with anti-streptococcic serum. Three of

the cases were bronchitis, with streptococci in the sputum, three were erysipelas, three scarlatina and three septic angina. In three of the cases there were rheumatic symptoms in addition to the local infections. In all cases the benefit from the serum was marked, and recovery was obtained in each case. The dose was 10 c.c. repeated every four to eight hours.

Ritter (Berlin. klin. Woch. 1909, xlvi, 634) speaks of the occurrence of streptococci in diseases of children, and of their treatment with anti-streptococcic serum. The streptococci do not often occur without the staphylococci in localized suppurative processes, and in these the treatment directed against the staphylococci is of the greatest importance. The author has never found a pure streptococcic infection in tonsillitis, but in cases of malignant sore throat they were generally present. In 117 cases of articular rheumatism, streptococci were found in the tonsils thirty-three times. In 10 per cent. of the suppurative skin diseases, impetigo and pemphigus streptococci were demonstrated. In 100 cases of ulcerated stomatitis, streptococci were found twenty-three times. The organisms were rarely found in enteritis or whooping cough. In diphtheria they are very commonly seen in conjunction with diphtheria bacilli. In scarlet fever they are evidently of great pathogenic importance. It has been only in mild cases that the organisms were not found. In erysipelas and infections of wounds they are always present.

Twenty-two children with erysipelas in different parts of the body were treated with anti-streptococcic serum, the dose being 2 c.c. per kilo of body weight. All these cases were under control by the second day, and 80 per cent. of them free from fever. The remainder were entirely free from fever on the third day of treatment. There were no disagreeable phenomena, except slight urticaria, which was not marked as that following the injection of diphtheria serum. In 87 cases which had been previously treated by other means, the shortest duration of fever was four days, and some of the cases lasted more than two weeks. In addition to these cases of erysipelas, four cases of umbilical sepsis in infants were treated with serum. These were all far advanced, the patients all being very ill when they came under observation, and all four died. The serum is of greatest service in severe angina. Thirty-four cases of mixed infection of the throat with streptococci were treated. In all these cases there was rapid disappearance of the psuedo-membrane, and within thirty-six to forty-eight hours the temperature had fallen to normal. Whoever has seen the threatening aspect of such cases will realize how good are these results. In scarlet fever cases with the presence of streptococci, 19 cases were treated, with 10 deaths, all 19 being very severe cases. In 14 cases of septic diphtheria with streptococcic infection, the diphtheria serum was followed by the use of anti-streptococcic serum, with ad-

vantageous results. All of these cases would probably have died under ordinary methods of treatment. Six of them recovered under the serum treatment.

Smith (Med. Rec. 1904, i, p. 533) reports six cases of pustular smallpox treated with anti-streptococcic serum; 20 c.c. were given at each dose, repeated every twenty-four hours. In these cases there was none of the general debility which followed the disease in former cases. The serum treatment shortens the course of the disease, prevents secondary infection, prevents pitting, and lessens the danger of lung and kidney involvement. If used early, the benefit is very striking.

Cerrada (Muen, med. Woch. 1909, lvi, 198) speaks of the treatment of febrile tuberculosis with anti-streptococcic serum. He has treated nine cases with such injections. In five cases there was no particular benefit. In three advanced cases the sleep, appetite, and night sweats were favorably influenced. In an initial case there was apparently marked and lasting improvement from the treatment. In each case two injections were given.

Boucheron (Gaz. Heb. de Med. et de Chir. June, 1898) uses anti-streptococcic serum in the treatment of rheumatic iritis. He gives $\frac{1}{2}$ c.c. the first day, and 1 c.c. on each succeeding day. In acute cases from three to six injections are necessary. In chronic and long-standing cases there is some improvement of sight and a more rapid absorption of exudates. The

serum exercises action on the streptococcus, and also acts as a stimulant to the nervous system in the same way as normal serum.

Carrieu and Palen (Gaz. deg. Osp. e delle Clin. May, 1908, 607) report a case of a soldier attacked with severe influenza, complicated by symptoms of meningitis and pleuro-pneumonia. Streptococci being found in the sputum, four injections of anti-streptococcic serum of 20 c.c. each were given with the result of completely subduing the fever, against which both quinine and antipyrin had proved inefficacious.

Strepto-Bacterin—Local Infections. Gildersleeve (Mo. Cy. and Med. Bul. 1908, 607) states that local streptococcic infections, both primary and secondary to tuberculosis, are markedly benefitted by the use of strepto-bacterin.

Beebe and Medalia (Bost. Med. and Surg. Jour. 1908, iii, 85) report a case of abscess in the neck due to the streptococcus, which was treated with strepto-bacterin. At the time of the first injection of 50,000,000 the patient was very weak, exhausted, pale, and emaciated, and there was considerable discharge from the wound. A week later the discharge had ceased and the wound was nearly closed. The patient had greatly improved in strength and appetite, and her color was good. Another injection of 50,000,000 was then given, and a week later the wound was entirely healed, with no induration around it. Four weeks later the patient had gained five pounds in weight, and was feeling perfectly well.

Erysipelas—Harris (Practitioner, 1908, 647) reports a case of erysipelas treated with streptobacterin. The inoculation was given on the sixth day of the disease, when the temperature was 105.4° , the pulse 140, the respiration 45, and the patient in imminent peril. This was followed by recovery by crisis, the temperature falling to 98.8° , fourteen hours after the injection.

Duncan and Ilman (N. Y. Med. Jour. 1908, ii, 552) report three cases of erysipelas treated by streptobacterin. The dose varied from 30,000,000 to 60,000,000. The first case was one of facial erysipelas, in which a dose of 50,000,000 streptococci was given on the sixth day. Twelve hours later the temperature fell, and from that time recovery was eventful. Previous to the injection being given, the lesion was spreading rapidly.

The second case was also facial erysipelas, and the patient's condition was growing worse. On the third day of the disease an injection of bacterin was given, and by the morning of the next day the temperature was nearly normal and there was marked improvement in the condition of the patient, who felt so much better that he insisted on leaving the hospital.

The third case was one of facial erysipelas following tonsillitis. The condition improved at first, but after it had existed for a week the inflammation began to spread rapidly. It spread continuously down the chest, reaching below the breasts, and on both arms. The

temperature to 105.2° , and the patient was frequently delirious. At this time strepto-bacterin was given. The next day there was considerable fall in temperature. There was no further extension of the inflammation and on the third day the temperature was only a fraction above normal. The following day the temperature was normal, and from that time the recovery was uneventful.

Schorer (Am. Jour. of Med. Sci. 1907, i, 728) reports 37 cases of erysipelas treated with strepto-bacterin. A study of the opsonic index shows that this rises until the third day of the disease and then gradually falls. Of the 37 patients three died, these cases being complicated with some other disease in addition to erysipelas. On the whole, the course of the disease seemed to be shortened and the local condition was improved. The dose varied from 25,000,000 to 100,000,000. Those receiving 25,000,000 showed desquamation three days after the injection. Those receiving 100,000,000 desquamated two and a half days after injection. The migratory form of the disease was seen in eight of these patients. The tendency toward this form of the disease was probably not induced by the injections.

Ross (J. A. M. A. 1909, Mar. 6) reports the results of treatment of 50 cases of erysipelas with strepto-bacterin. He believes that the treatment exercises a specific and controlling influence upon the course of the disease, lessening its severity, preventing the spreading of the lesion and

hastening recovery. The opsonic power of the blood was low during the acute process, while the infection was spreading. After the injection of bacterin there was a rise in opsonic power, manifested clinically by the subsidence of malaise, mental restlessness or apathy pain, and tenderness, and by the localization of the inflammatory area. The author has frequently observed parallel series of events in bacterial inoculations for erysipelas, septic inflammation of the hands, and surgical tuberculosis. The evidence adduced in this connection was, he believed, sufficient to justify the use of bacterins prepared from the streptococcus in the treatment of erysipelas. In the first 16 cases of the 50 reported the opsonic index was taken, but as the clinical symptoms varied parallel to it, it was omitted in the other cases. In certain severe cases a blood examination is advisable. It is unnecessary to prepare a bacterin for each case, but it is advisable to have a complete stock bacterin made from several strains and as many cases as possible. An injection of 10,000,000 killed bacteria is given when the case is first seen; 20,000,000 is given if the case is not severe. At the second injection the patient gets 10,000,000 more, if there has been any improvement. If no evidence of improvement follows, only 5,000,000 should be given at the second injection. In the less severe cases improvement is almost always manifest on the day after injection. The author then inoculates with from 5,000,000 to 20,000,000

streptococci every second day until a week after the temperature has reached normal and the erythema has subsided. The rule is, "The more severe the case and the less satisfactory the clinical response the smaller the dose. "The site of injection was always chosen at a distance from the inflammatory area. The results have always been so satisfactory that it has not been thought necessary to attempt inoculation near the site of infection.

Puerperal Sepsis—Lloyd (Intercol. Med. Jour. of Austral, 1907) reports the following cases of puerperal sepsis, which were found to be mixed infections with staphylococci and streptococci and were treated with mixed strepto-staphylo-bacterin.

The first case showed a temperature of 105° and a pulse of 136 on the eighth day after delivery. Cultures showed the presence of streptococci and staphylococci, and the injections were given of 25,000,000 streptococci and 250,000,000 staphylococci. Seven injections were given, at intervals of two days, doubling the quantity at each injection. On the fortieth day the patient was sufficiently improved to leave the hospital.

The second patient showed a temperature of 103° and a pulse of 168. Two days later a culture from the uterus showed the presence of streptococci and staphylococci. The uterus was swabbed with 2 per cent. formalin and packed with iodoform gauze. As the patient's condition continued to grow worse a bacterin

was made and an injection of 100,000,000 cocci was given. From this time the progress was satisfactory, and the patient was soon convalescent.

Castler (*Am. Jour. of Obst.* 1909, 594) reports a case of puerperal sepsis treated by mixed bacterins. The patient was admitted to the hospital three days after a miscarriage, with a temperature of 101° and pulse of 100. In spite of operation for the removal of pus tubes and energetic local treatment, the discharge continued to be very abundant. The abdominal incision refused to close, and a secondary operation with posterior drainage was unsuccessful. During all this time the temperature ranged from 99° to 103° , and when the bacterin treatment was commenced the patient was much emaciated and very anemic, with all the symptoms of chronic sepsis. Injections of 90,000,000 streptococci and 150,000,000 staphylococci were given every third day for four weeks. Almost from the first injection there was a noticeable general improvement in the patient. The temperature and pulse began to fall, and at the end of three weeks the temperature was normal.

Mixed Infection—Vanderhoff (*Ill. Med. Jour.* 1909, 686) reports two cases treated with strepto-bacterin, and says that he knows of other cases in which it has been used with great benefit. These cases were both rheumatic iritis. The first case had had pain in the eye for seven days when an injection of 30,000,000 streptococ-

ci was given. Previous to this time the patient's condition had grown steadily worse. The day after the injection the patient felt better, and there was less pain. From this time there was rapid improvement, and in a few days he returned to his work. Soon after starting at work the eye became worse again, but after a second injection of streptococcic bacterin the iritis immediately quieted down, and has caused no trouble since.

The second case was much the same, and the disease had also been in existence a week before the first dose of 30,000,000 was given. The next afternoon there was a marked change for the better. The pericorneal injection was much less, and the patient could open his eye for the first time in several days. The case from this time recovered rapidly, only one injection being used.

These two cases are simply examples of the good results which are frequently derived from the use of the bacterin treatment. The results have been particularly good in acute streptococcic and staphylococcic infections of the ear, nose and throat. The author states that his results have been negative in chronic suppurative conditions of the sinuses, but is not able to say whether or not this is due to his not having continued the treatment long enough. He considers the bacterin treatment very valuable, and thinks that the bacterins should be kept in the office of every physician, especially those in the country.

Williams (Am. Jour. of Obst. 1908, 152) states that strepto-bacterin has been used on a number of tubercular gland and joint cases, with the hope of influencing secondary infection. Injections have been given in 35 cases of adenitis, in two of which there was a marked immediate improvement, with rapid recovery; and there was apparently some improvement in several other cases. In 15 joint cases, all showed improvement following the injections. In one case of peritonitis and arthritis, which had an absolutely bad prognosis, there was an immediate change for the better after the first injection, and the patient became convalescent. Although the cases have been too few to draw positive conclusions, the results have been very encouraging.

Septicemia—Hartwell, Streeter and Green (Surg. Gyn. and Obst. 1909, ix, 271) state that they have treated 97 cases of sepsis with bacterins. The initial dose varied from 5,000,000 to 25,000,000, the dose being increased with each successive injection. The maximum amount given was usually 100,000,000. In each case an arbitrary interval of four days was made between inoculations. A bacteriological examination was made, and each case treated with staphylo-bacterin and strepto-bacterin, or with a mixed bacterin containing both strepto and staphylococci, according to the pathological report. In many cases anti-streptococcic serum was used before the bacterin treatment was started but the results from the bacterin

treatment were better on the whole, than those following the use of the serum; 24 of the cases were general infections, 18 of these being puerperal. All of the 18 cases recovered; 22 cases were septic abdominal wounds, and none of these were in bad condition at any time. Infection was generally mixed, and corresponding mixed bacterins were used. A third group of 41 cases were all local sepsis, 25 of these being streptococcic infection. All recovered, some after extensive incisions. The fourth group does not include any cases of streptococci infection. The author concludes that:

1. Bacterial vaccines should be employed in cases of puerperal infection which do not respond promptly to routine treatment.

2. Bacterial vaccines are especially useful in cases which have remained stationary for some time.

Thompson (J. A. M. A. 1909, i, 1781) read a paper before the Association of American Physicians, May 11, 1909, in which he stated that he had treated seven cases of septic endocarditis and one of pyemia with streptobacterin, "with results which have demonstrated its effectiveness." Three of the patients with septic endocarditis were cured, as was the one with pyemia. In several other cases of septic endocarditis there was evidence that the septic process had been entirely controlled, although death ensued from such complications as tuberculosis or pneumonia. In none of the cases in which homologous bacterins were used

was there failure to produce improvement, such as fall in temperature. Several cases which came under treatment after months of illness in condition in which fatal issue seemed imminent, gave signs for many weeks of arrested progress of the disease. The three patients who recovered from endocarditis had a type of the disease in which the author had never previously seen recovery take place. The dosage of bacterin varied from 50,000,000 to 300,000,000 at intervals of two, three and four days, according to the circumstances of the case.

Farbach (Ky. Med. Jour. 1908, 688) states that he has used strepto-bacterin in one case of acute and one case of chronic streptococcic infection. The acute case was a septicemia, with a temperature of 105° and a pulse so rapid that it could not be counted. Within five hours after the first inoculation the temperature was subnormal and the pulse greatly improved. The patient eventually made an uneventful recovery. The chronic case was characterized by groups of large carbuncles. After three inoculations all the lesions had disappeared, and the patient's general condition was greatly improved.

Bristow (Med. Rec. 1908, i, 199), in a paper read before the Medical Society of New York, January 28, 1908, stated that he had used the strepto-bacterin in a series of cases, a few of which he reported. The first case began with an abscess of the superficial cervical glands, which was followed by phlebitis of the femoral

vein and septic endocarditis. This was followed by convulsions. After the first convulsion an injection of 5,000,000 strepto-bacterin was administered and the next day the temperature had fallen, but there was another convulsion. Eight days later an injection of 10,000,000 was given. From this time the patient steadily improved and soon recovered good health.

The second case was admitted to the hospital with a diagnosis of acute rheumatism with acute endocarditis. A blood culture revealed the presence of streptococci. The patient received two or three doses of anti-streptococcic serum without benefit. Soon after, an injection of 5,000,000 stock bacterin was given. Two days later 5,000,000 were injected. From this time on the patient improved and recovery was uneventful.

The third case was one of furunculosis, lasting for two years. The streptococcus pyogenes aureus was isolated from the lesions. After the use of strepto-bacterin the condition cleared up and the patient remained free from furuncles for four months, when she had a single boil, which cleared up after the injection of bacterin.

Van Cott (L. I. Med. Jour. Ed. 1909, 219) states that in cases of sepsis he formerly used autogenous bacterins because of the uncertain bacteriological nature of these cases. Recently he has used with equally good results a polyvalent bacterin, containing streptococci, staphylococci, and colon bacilli. This mixed bacterin has proved of especial value in puerperal

sepsis. It has the great advantage that no time is lost in the preparation of the bacterin. With the use of this bacterin the author feels that the prognosis is good in the majority of cases.

Prevention of Infection.—Richard M. Smith (Bost. Med. and Surg. Jour., 1910, i, 242) reports in some detail the literature on the subject of preventive inoculation of scarlet fever. He states that the first work which was done on this treatment for the prevention of scarlet fever was that of Steckler (Med. Rec. 1883, xxiii, 316), who, in 1883, injected the blood of a scarlet fever patient into himself and three days later had a scarlatina eruption, followed by desquamation. He then took desquamated scales from scarlet fever patients and injected them into healthy individuals. He found if the serum was later injected into such persons, no reaction was caused.

The next work was reported in 1905 by Gabritschewsky (Russ. Vrach. 1905, No. 30), who obtained good results in the prevention of scarlet fever by the use of streptococcic bacterin. His work was based on that of Klein (Rep. of Med. Off. Loc. Brd. of Gov. 1885-86) and others, who had shown the importance of the streptococcus as the causative agent in scarlatina. Gabritschewsky claimed that after three doses of the bacterin—and usually after two doses—complete immunity was established against scarlet fever. This immunity is not complete until five to seven days after the last dose, although a relative immunity probably exists

from a week after the first injection. The immunity lasts probably anywhere from six to eighteen months. Twenty-four hours after the first injection there appears at the site of inoculation an area of redness, which is slightly tender, and lasts from one to three days. Rarely there is some headache, or general malaise. In 10 per cent. of the cases there appears an erythema over the body, resembling a very mild scarlatina eruption. After the second and third injections which are given at intervals of a week, there is usually no reaction.

Smirnoff (Vrach. Gaz. 1909, xv, 368) used bacterin in thirteen small villages in Russia, where the sanitary conditions were very poor and where there was no possibility for quarantine. In the villages in which he used it no new cases were reported two weeks after the treatment was instituted, while in the other villages the epidemic continued for upwards of two months. In these villages Smirnoff inoculated 127 children, of whom only five took the disease, three of these being infected before the second inoculation; 91 children were not inoculated, and of these 36 were infected with scarlet fever, being about 40 per cent. Altogether he inoculated 455 persons, and among these there were only seven cases; five of these occurred after the first injection, two after the second, and none after the third. There were no deaths among the inoculated cases, as compared with 11 per cent. mortality among the uninoculated.

Yemelanoff (Vrach. Gaz. 1909, xv, 364) reports an epidemic in which eight or ten new cases were being reported every day and nearly every house in the village was infected. Quarantine regulations could not be enforced; 610 cases were inoculated and of these not a single one contracted the disease. It was possible to keep the schools open, even though the children came from infected houses.

Dorofeyeff (Vrach. Gaz. xv, 366) reports the results in three small villages. He injected 142 persons, two of whom took scarlet fever after the first injection. There were no cases after the second injection. These two cases were both very mild and without complications, although in the uninoculated cases 80 per cent. had nephritis.

Zelikin (Vrach. Gaz. 1909, xv, 372) reports a severe epidemic in which there had been 210 cases, with a mortality of between 30 and 40 per cent. He inoculated 741 persons. Four had scarlet fever, all before the second inoculation.

Markuzon (Prakt. Varach. 1907, vi, 292, 315) in 1906, inoculated all cases admitted into the hospital under his care, except those which had very high temperature, those showing nephritis, very young infants, and extremely debilitated cases. In patients with typhoid fever, pneumonia and other acute infections, the inoculations had no effect on the course of the disease, causing only a temporary rise in temperature.

Lifshits (Orakt. Vrach. 1907, vi, 773, 793) during a severe epidemic inoculated 170 cases. Only three of these took scarlet fever, all after the first inoculation.

Nikitin (Russ. Vrach. 1907, vi, 989) inoculated 783 cases, among whom there were only eight cases of scarlet fever, all being in persons who had received only one inoculation. In the villages where inoculation was not practiced, 16 per cent of the children had scarlet fever, while in the villages where it was practiced only 1.4 per cent took the fever.

Akaporoff reports 308 inoculations, with three cases of scarlet fever, all after the first inoculation.

Perwoff (Russ. Vrach. 1907, vi, 989) reports 282 cases inoculated, only two of which took the disease, both after the first inoculation.

Neurzoft inoculated 173 persons exposed to scarlet fever, and only two cases occurred among the series, both occurring the second day after inoculation.

Schwarin (Russ. Vrach. 1907, vi, 891; Vrach. Gaz. 1909, xv, 367) inoculated 497 cases, only two of which subsequently took scarlet fever.

Dobensky injected 132 cases, none of which took the disease.

Langovoy (Centralbl. fur. Bakt. 1906, xlii, 362, 463; Russ. Vrach. 1906, x, 565) inoculated all persons admitted to a hospital in Moscow, where during the four previous years three per cent of the children in the wards had had scarlet fever. Since the inoculation treatment, cov-

ering a period of several years, only four cases among 309 patients developed scarlet fever, a little over one per cent.

From these published accounts it is evident that:

1. The streptococcic bacterins have some influence in controlling epidemics of scarlet fever.

2. They should be given wider application in this country.

Tuffier (*Presse Med.* 1909, p. 689) considers the use of streptococcic serum as a means of preventing postoperative infection. He says that the immunity produced by the use of serum is immediate, and reaches its maximum in twenty-four hours. Renne injected 10 c.c. three hours before operation for extensive abdominal cancers. In 12 operations, one patient showed suppuration, and one died of septic peritonitis. On the whole, it would seem that the method has less value than the use of bacterins injected a few days before operation.

CHAPTER XIII.

Bacterins.

(Continued)

Typho-Bacterin.—Quoting from Working Bulletin No. 6, the following information is obtained :

History.—The first work on inoculation treatment of typhoid fever was done by Frankel (Deut. med. Woch. 1893, xix, 985) who published in 1893 an article on the treatment of typhoid fever with a killed culture of typhoid organisms. Although his results were favorable, nothing further on the subject appeared until 1896, when Pfeiffer and Kolle (Deut. med. Woch. xxii, 735) observed the production of antibodies following the inoculation of dead bacteria.

Later in the same year, Wright (Lancet, 1896, Sept. 19) published his first articles on the subject of anti-typhoid inoculation, and from that time on, articles flowed steadily from his pen. Being connected with the British army in India he was able to introduce the method of protective inoculation into the Indian army, and his results showed the value of the method.

In 1900 the Prussian War Ministry studied Wright's figures and came to the conclusion that the method was a very valuable one and should be introduced into the German army in the tropics.

Jez (*Wein. Med. Woch.* 1899, xlix, 345) attempted to overcome the reaction which follows inoculation by mixing his killed culture with a serum prepared from the glandular and nervous tissue of immunized animals. Palladine-Blandini (*Rif. Med.* 1902, i, 746) separated the nucleo-proteids of the typhoid bacilli and used them for inoculation purposes. In the same year Besredka (*An. de l'Inst. Pasteur*, 1902, xvi, 918) prepared an inoculation material by mixing a culture of typhoid bacilli with an immune serum and using the sensitized bacilli.

Wasserman (*Zeit. fur Hyg.* 1892, xii) Neisser and Sheiga (*Berlin klin. Woch.* 1904, No. 4; *Deut. med. Woch.* 1903 No. 4) and Bassenge and Mayer (*Deut. med. Woch.* 1905, xxxi, 697) used filtrates prepared from typhoid cultures by special procedures. In this country Vaughan (*N. Y. Med. Jour.* 1907, i, 1170) showed that the typhoid bacilli could be separated into a toxic and non-toxic portion, and that inoculation of the latter had a certain protective power.

Hesch and Kutscher (*Klin. Jahrb.* 1905, xiv, 146) determined the protective powers of the toxins of Wasserman and Neisser-Sheiga, the methods of inoculation of Pfeiffer-Kolle (inocu-

lations of 1 oese, 2 mg., of an agar culture) and of Bassenge-Rimpau (2 injections of respectively 1-30, 1-15, and 1-5 oese at intervals of ten days) and the method of Wright. The protective powers of the Wasserman, Neisser-Shiga, and Bassenge-Rimpau methods were found to be insufficient. The constitutional reaction was much less marked, but the local phenomina were much the same as after the use of other methods. The effects of the Wright and Pfeiffer-Kolle methods were much the same in regard to reaction and protective power. The protective power in each case was determined by the rise in the antibodies. Hetsch and Kutscher concluded that the Wright and Pfeiffer-Kolle methods were apparently equal in protective power, while the other methods are decidedly inferior.

Summary.—It will be seen from these articles that the protection obtained by the inoculation of the various extracts of the bacilli is not as great as that obtained by the inoculation of killed cultures, and this method has, as a result, been adopted almost universally as a method of choice. There is no longer any doubt as to the value of the injections as a means of protection against typhoid infection, and the severity of the reaction is not sufficient to discourage the use of the inoculations. The reaction is limited at the present time by injecting first a small amount, and ten days later, when the antibodies have appeared in the blood, injecting a larger dose which will give full pro-

tection. The value of the method has been repeatedly demonstrated, both statistically and by determination of the antibodies in the blood after inoculation.

Vaccine Treatment.—Allen (*Vaccine Therapy and Opsonic Treatment*, Fourth Edition, 1913, pp. 206-219) gives the following information relative to the vaccine, or bacterin, treatment of typhoid fever:

Inasmuch as the portal of entry in this disease is through the intestinal tract and the principal lesions are there situated, it is most conveniently considered now instead of in its, perhaps, more correct place among the septiciemias.

Bacteriology.—In view of the fact, which is becoming increasingly clearer, that a percentage of cases, by no means inconsiderable is due to organisms other than the true *B. typhosus* of Eberth, exact determination should be made of the infective agent in all cases, whether vaccine treatment is contemplated or not. To the two varieties of organisms most closely allied to the *B. typhosus*, the names *B. Paratyphosus A* and *B* respectively have been given; to other varieties, which may give rise to conditions resembling typhoid fever in many respects, the title of 'paracolon bacilli' has been given, in virtue of a closer relationship to the *B. coli communis*. Although the primary lesions are situated in the intestines, a condition of septicemia is very soon established, and blood cultures yield a positive result in almost every

case after the first two or three days. The bacteria disappear from the blood with some rapidity, so that by the end of the first week a much smaller percentage of positive cultures is obtained, even when large quantities of blood are utilized. Subsequently the bacteria may have to be isolated from the feces or urine.

The organism so obtained is identified by means of its sugar reactions, and confirmation of its identity made by comparative serum tests with this organism and another known one to which it is supposed to be similar.

If an autogenous vaccine is prepared, it should be remembered that sterility must be secured either by heating at 53° C., but not over, for half an hour, and the addition of 0.2 per cent tricresol, or, as Semple recommends, by the action of 0.5 per cent carbolic acid alone, this being effective within twenty-four hours. If any greater degree of heat than 53° C. be employed, not only are the keeping properties impaired, but the immediate immunizing power is lowered.

General Considerations.—* * * * the body elaborates various antibodies to the B. typhosus—viz., agglutinins, lysin, and opsonin. The relative importance of these bodies is not definitely known. Formerly the chief protective role was ascribed to lysin; now the greater importance is assigned to opsonin and phagocytosis. By lysis the discharge is brought about of powerful endotoxins into the circulation, and it is to this cause that the continuous pyrexia

of the early stages of the disease is due. The intermittent temperature of the later stages is probably due in part to the absorption of other toxins from the ulcerated surface of the Peyer's patches, and in part to the liberation of endotoxin which occurs when bacilli are dissolved before being ingested. The therapeutic use of powerful lytic sera may be fraught with danger owing to the liberation of excessive quantities of endotoxin; the therapeutic use of anti-endotoxic sera may be found to modify the severity of the disease by neutralization of the endotoxin, and the therapeutic use of vaccines, by stimulating the formation of opsonin, may be expected to influence the disease by bringing about the more speedy extinction of the bacteria within the phagocytes, the endotoxins being destroyed therein instead of being set free in the general circulation. Its good effects are, however, limited owing to the fact that in those situations where the bacteria are mostly stored (viz., spleen and Peyer's patches) there is exhaustion of the opsonin, and local conditions tend to nullify the effect of increased opsonin elaboration. It is also possible that 'complement' may be in defect, and this we know not how to make good.

Agglutinin probably plays a very subsidiary role, but, as we have seen, its amount is not devoid of prognostic import. The curves of agglutinin, lysin and opsonin, run a more or less parallel course, and inasmuch as opsonic index determinations are more than usually difficult

in this disease, the "agglutinin" curve is often substituted as a guide to the progress of immunization. In the practice of vaccine treatment reliance is now, as a rule, placed for guidance on the temperature chart and the clinical signs and symptoms.

Vaccine Treatment.—For a full account and discussion of the results obtained by himself and other observers, the reader should consult an article by Sir David Semple (*Jour. of Vaccine Ther.* Feb. 1912). Papers by Stoner (*Am. Jour. of Med. Sci.*, Feb. 1911), Callison (*N. Y. Med. Jour.*, July 15, 1911), Watters and Eaton (*Med. Rec.*, May 6, 1911), Makins and Forster (*Can. Med. Jour.*, June, 1911), Smallman (*Jour. of Roy. Army Med. Corps*, vol. xii, p. 136), and Engelbach (*Interstate Med Jour.*, June, 1912, p. 537), will also afford useful information.

The procedures adopted by each differs in regard to dosage and intervals. Thus Semple originally began with initial dose of 6,000,000 to 50,000,000, but now recommends 100,000,000, this being gradually increased to 200,000,000 or 300,000,000. These he gives daily or on each alternate day, according to the clinical response. He thinks that occasional estimations of opsonin and agglutinin are useful. Callison originally employed 25 000,000 but now prefers 300,000,000, and employs estimations of opsonin and agglutinin as a guide to the progress of immunity. He believes that negative phases after such doses are either non-existent or a negligible quantity. Meakins and Forster use

1,000,000,000 as a first dose, 1,500,000,000 as the second about eight days after the first and 2,000,000,000 as the third dose after a similar interval. Smallman, in his earlier cases, used 100,000,000 as his first and second doses, the interval being nine or ten days. Later he used doses of 300,000,000 at shorter intervals with better results. Sadler (*Jour. of Vacc. Ther.* vol. i, No. 1, p. 17) prefers an initial dose of 2,000,000, a second five days later of 1,000,000, this dosage and interval being continued subsequently. Alternatively he advocates doses of 300,000,000.

Summarizing the matured opinions of those who have had the greatest experience, it would appear that the best initial dosage is one of 250,000,000 to 300,000,000, which may be safely repeated at intervals of three to five days, according to the immunizing responses and the clinical condition of the patient.

There is some difference of opinion as to whether "stock" or autogenous vaccines give the best results. Some prefer a stock vaccine made from a strain such as we shall see is employed for preparing the vaccine for antityphoid immunization, viz., a long-cultured strain which has lost almost all pathogenic powers but still possesses a strongly immunizing action. Others prefer a polyvalent vaccine made from fully virulent strains, not only of the *B. typhosus*, but also of the paratyphoid bacilli. Others much prefer the autogenous vaccine in every case. Inasmuch as mixed infections by

the *B. typhosus* and a paratyphoid bacillus are not unknown and purely paratyphoid infections are fairly common, I think the wisest procedure is to employ for the first dose or two a stock polyvalent vaccine containing the *B. typhosus* and paratyphosus, proceeding meanwhile with the preparation of the autogenous vaccine and to utilize this for subsequent inoculations.

The Results of Vaccine Treatment.—The immediate results of inoculation with a vaccine are best seen in the severely toxic cases. Within twenty-four hours there should be, in the majority of instances, a decided improvement in the general condition, a lowering of the temperature and pulse-rate, a clearing of the mind and evidence of greater comfort of the patient. A retrogression in any one of these directions is the signal for reinoculation. Occasionally improvement is delayed until the second day; in this case reinoculation may be deferred for two or three days, or until retrogression is observed; but if no improvement is discerned by the end of forty-eight hours, the immediate administration of a double dosage is advisable. Treatment should be continued till the lapse of three or four weeks after complete defervescence, in order to secure the destruction of any bacilli which may still be lurking in the tissues.

The observed influence of vaccine treatment upon the mortality and liability to relapse are best shown in tabular form on page 244.

The number of cases so far recorded is too small to allow of a definite comparison being

drawn between the results obtained by treatment with vaccines, and those obtained when treatment is conducted according to the usual routine principles. Both the mortality rate and the percentage of relapses vary greatly from time to time. The former varies between 10 and 20 per cent., the mean of 15 per cent. being a fair average. Relapses occur on the average in 20 to 25 per cent. of cases. The figures given below—viz., 4.1 per cent. for the death rate and 3.9 per cent. for relapses, would seem to leave a very appreciable balance to the credit of vaccine treatment.

Observer.	Cases	Deaths	Relapses	Per Cent. of Deaths	Per Cent. of Relapses
Sample	60	2	2	3.3	3.3
Stoner and Callison	266	12	11	4.5	4.1
Watters and Eaton	36	..	3	..	8.3
Meakins & Forster	41	1	1	2.4	2.4
Smallman	36	3	..	8.3	..
Total	439	18	17	4.1	3.9

The unanimous opinion is that vaccines are quite innocuous when properly used, and that no aggravation or injury of any kind results from their use; but that, on the contrary, they confer distinct benefits on the patient, by diminishing the toxemia, shortening the duration of the disease, reducing the mortality and diminishing the liability to relapse.

Typhoid Carriers.—As the amount of study that is devoted to the elucidation of the causa-

tion of typhoid epidemics accumulates, the more increasingly clear does it become that in many instances such epidemics are initiated by contamination of the food and drink at the hands of those who prepare or supply it. These individuals continually harbor the *B. typhosus* somewhere in their bodies, usually in the gall-bladder or kidneys and are accordingly known as "carriers". In the great majority of these a history of definite attack of typhoid fever is usually obtainable. As a rule, convalescence is uninterrupted, though perhaps rather prolonged, and recovery apparently complete. The detection of these carriers is thus a matter of great concern. It is likewise one of no little difficulty owing to the fact, first demonstrated by Semple, that the discharge of bacteria may be very intermittent. It has been stated that it is impossible to declare with certainty that anybody who has recovered from an attack of typhoid fever has not become a carrier unless careful bacteriological examinations of the urine and feces, conducted at weekly intervals for at least one year, fail to detect the presence of the bacilli. Semple's view that the storage of organisms takes place in the liver and kidneys has been confirmed by numerous other observers. Some of the investigations are of particular interest. Alice Hamilton (*J. A. M. A.*, Feb. 26, 1910, p. 704) examined twenty-four persons with a history of gall-bladder trouble. Determinations of the opsonic index of the sera, after these had been heated at 58° C. for fifteen to

twenty minutes, showed that seven out of the twenty-four had constantly abnormal indices to the typhoid or paratyphoid bacillus. Of these, those who had acute gall-bladder symptoms had a fluctuating index the others a persistently high one. All these seven individuals were proved to be carriers, five of a paratyphoid bacillus, two of the *B. typhosus*. In only five out of the seven was the Widal reaction obtained. Of the seventeen non-carriers, none had abnormal index nor gave a Widal reaction in a 1 in 50 dilution. Hamilton claims that index determinations are trustworthy and much simpler than bacteriological examinations of the urine and feces.

It has occurred to me that much the simplest method of detection would be to do a "Calmette's reaction" on the eye using, not an emulsion in water of the dead bacillus, as has been done for the diagnosis of active typhoid fever, but a preparation of endotoxin made by MacFayden's method. In order to prove the reliability of this method, it will be necessary to make comparisons in a large number of cases, not only of those who are shown by direct observation to harbor bacillus, but also those who have made complete recoveries.

Although the liver and kidneys are the chief lurking-places of the *B. typhosus*, they are by no means the only ones. Thus Cammidge (*Lancet*, Jan. 19, 1909, p. 1739) records the detection of the bacillus in the stools of a case of pancreatic glycosuria, a sufferer ten years previ-

ously from typhoid fever. In this case the nidus would appear to be in the pancreas. The bacilli have also been recovered from bone abscesses, which have appeared long after apparently complete recovery from typhoid fever. Sir Hector Cameron (Br. Med. Jour. April 29, 1911, p. 975) records one such case twenty-seven years afterwards. Other cases have been recorded six and ten years afterwards. It is an interesting question whether the routine treatment of typhoid fever, by means of vaccines, well into convalescence would not do much to diminish the number of these carriers, the existence of whom is such a source of continual danger to the whole community.

Vaccine Treatment of Carriers.—Ordinary methods of treatment have proved entirely ineffectual in these cases, but in a few instances success has attended vaccine treatment. The first case to be so treated was reported by Irwin and Houston (Lancet, Jan. 30, 1909, p. 311). It was that of a carrier of seven years' duration, who was excreting large numbers of bacilli in the urine, but none in the feces. An injection of 50,000,000 produced rise of temperature, malaise and headache. Double this dose eight days later produced a milder reaction, and was followed eighteen days later by one of 200,000,000. Two days after the third injection the urine was crowded with bacilli. The urine was rendered alkaline, and eighteen days later the *B. typhosus* had disappeared from the urine. Further doses of 300,000,000, 500,000,000 and

1,000,000,000, were given at intervals of fourteen days. The agglutination test was only obtainable then in the 1 in 10 dilution, instead of in one of 1 to 200, as formerly. There was considerable improvement in the general health, and the patient gained 10 pounds in weight. Although observations have been made of the urine for over two years, the *B. typhosus* has never again been detected. Houston (*Br. Med. Jour.*, 1909, vol. ii, p. 1056) has since treated three more similar cases. In two of these complete cure appears to have been brought about, the other one has been markedly improved.

Inasmuch as results equally successful with those obtained by Houston have been achieved by Dickson (*Ulster Md. So.*, May 10, 1911) and other observers, it would appear that in vaccines we have the only practical means of ridding "carriers" from their infection, though at times this treatment will also fail.

Antityphoid Inoculation—Methods of Preparing the Vaccine.—The method approved by the Army Council for use in the British Army is as follows: A layer of broth, 1 to 1½ inches in depth, is placed in special flasks of such form that maximum aeration is secured. The medium is inseminated with a special strain of the bacillus which has lost almost all its virulence, even for animals. Incubation is conducted at 37° C. for thirty-six to forty-eight hours, when the growth is sterilized at 53° C. for one hour, sterility being observed by means of aerobic and anaerobic cultures, and 0.4 per cent. of ly-

sol is added to insure absolute sterility. The vaccine is standardized in the usual manner in duplicate.

Semple advises that sterility should be secured without the aid of heat, and states that this is secured after twenty-four hours admixture with 0.5 per cent. carbolic acid.

Castellani prefers a vaccine which has been heated to 50° C. for half an hour. This contains still living but greatly attenuated bacteria.

Vincent advises the following procedure: The bacteria, which consist of typhoid and paratyphoid strains, are grown on a solid medium and removed therefrom and allowed to autolyze in 0.9 per cent sodium chloride solution. The mixture is well centrifugalized, and the clear supernatant liquid removed, mixed with ether, and well agitated, the ether being removed by heating to 37° C. for a few minutes. This vaccine is practically free of bacterial bodies, and is a solution of endotoxins.

The vaccine used in the English, French and American armies is prepared according to the first of these procedures; subsequent methods have been devised to improve the keeping properties, as when the first method is employed it is found that the power to incite the formation of opsonin, lysin, and agglutinin, begins to decline after three months, and falls off rapidly after six months.

The Procedure of Immunization.—This varies slightly in different countries, and with different authorities. The present procedure in the

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The American Commission on the Prevention of Epidemic is encountered. The first evidence of immunity thus conferred by the vaccine is given by Harrison (Jour. of Roy. Soc. Med., 1907, p. 472) and others. The definite evidence of increased immunity is given by the serum of men who had been vaccinated as long as six years previously. The results show that full immunity is maintained for two years.

Results of Immunization.—Much discussion has taken place in the past as to the merits

English army is to repeat the first dose of 500,000,000 on the tenth day; in the American army 500,000,000 and 1,000,000,000 are given in succession at intervals of nine days; in the French army four doses are given. Inoculations are given subcutaneously either at a point of the upper part of the chest, at a site about $1\frac{1}{2}$ inches below the center of the clavicle; high up on the buttock, about 2 inches from the middle line; or the side of the abdomen, about 2 inches inside the anterior superior spine of the ilium. Castellani, who formerly administered 0.5 c.c., 1 c.c. and 1.5 c.c. of his vaccine at intervals of a week, now advises that a 500,000,000 dose of vaccine prepared according to the first method should be followed a week later by 1 c.c. of his own preparation, and claims that thereby a higher degree of immunity is secured.

Effects of Inoculation:

1. **Locally.**—Tenderness begins to make itself felt in five or six hours, and is at its worst in about eighteen hours, when there may be developed redness over an area of two inches radius. Occasionally the lines of the lymphatics may be traced, and some tenderness of the corresponding lymphatic glands. These should all pass away within forty-eight hours.

2. **Generally.**—Some degree of malaise is usually produced. In a small percentage of cases there is a tendency to faintness; occasionally a rigor comes on between the first and sixth hours; rarely there is diarrhea, vertigo,

or a slight diffuse erythema. There is always a slight degree of pyroxia, usually to 100° F., occasionally to 101° F., and rarely to 103° F., which generally subsides by the end of twenty-four hours.

Formerly it was stated that there was a marked reduction of opsonin, lysin, and agglutinin, in the serum for several days, followed by a greater rise.

This "negative phase," which was formerly regarded as strongly contra-indicating immunization, either during an epidemic or when exposure to infection would occur within a few days, is now characterized by Leishman, Russell, and others, as a pure bogey. Thus Leishman points out that during a recent very severe epidemic at Maidstone, the attendants were all immunized at the time, yet not one contracted the disease; also that typhoid is always endemic in India, and that the garrisons are accordingly exposed to infection during immunization, yet no epidemic is encountered.

The duration of the immunity thus conferred has been studied by Harrison (*Jour. of Roy. Army Med. Corps.*, 1907, p. 472) and others. They have found definite evidence of increased antibodies in the serum of men who had been inoculated as long as six years previously. Leishman believes that full immunity is maintained for two years.

The Results of Immunization.—Much discussion has taken place in the past as to the merits

of the procedure. Recent evidence is, however, greatly in its favor. For instance, during maneuvers of the American army at San Antonio the whole strength of 12,639 men were inoculated, with the result that only one mild case occurred during the whole four months, although among the populace there were 49 cases and 19 deaths. Among a force of between 3,000 and 4,000 who were encamped at Galveston, and received the same food, milk, and water supply as the inhabitants of the city, there was not one case of enteric. Among the inhabitants during the same time there were 192 cases. During the preceding maneuvers in Florida, which were conducted at the same time of year and under precisely similar conditions, the water supply coming from an artesian well of accepted purity, 10,739 men, who were not inoculated, were engaged; 1,229 cases occurred, and 248 deaths; the significance of these figures is, however, in dispute.

In India, as the proportion of the army voluntarily undergoing immunization increases, it is noted that both the number of cases and of deaths show a steady and marked decrease; at the same time it must be admitted that the increased attention given to the "carrier" question cannot be without its effect. In the following table are set out the rates of typhoid fever, and of deaths therefrom, and the ratio per 1,000 of men inoculated in the army of India from 1906 to 1910 inclusive:

Year	Typhoid Rate	Death-Rate therefrom	Ratio of Men Inoculated per thousand
1906	15.6	3.19	66
1907	13.1	2.77	143
1908	14.5	2.76	225
1909	8.9	1.58	613
1910	4.6	0.63	823

Thus the typhoid rate has fallen in five years from over 15 to under 5 per 1,000, and the death rate from over 3 to 0.63 per 1,000. During 1910, among 70,000 men there was a total of 306 cases of enteric; 151 of these occurred in the 10,000 who were unprotected, and only 155 in the 60,000 who were. Only 11.2 per cent. of the inoculated died, and 16.1 per cent. of the uninoculated.

Finally, of the 16,496 men of the German army who took part in the Hereros campaign from 1904 to 1907, 7,287 were inoculated and 9,209 not. There were 1,277 cases of enteric altogether. Among the inoculated the incidence rate was 5.09 per cent. and the death rate 6.47 per cent. Among the uninoculated the incidence rate was 9.84 per cent. and the death rate 12.8 per cent. These various statistics must surely place the value of the proceeding beyond all further question.

Rabies Vaccine.—Although the process of immunization against rabies is not absolutely identical with that produced through the use of the bacterins, it is so similar in many ways as to place its discussion justly within this chapter. In his Text-Book on Pathogenic Bacteria, Fifth Edition, 1907, McFarland gives a

full and concise description of the treatment of the disease, through the Pasteur method of immunization, and which is quoted as follows:

For the cure of infected cases exactly the same treatment is followed as for the production of immunity. Indeed, the treatment of the disease is simply the production of immunity during the incubation period of the affection, so that the subsequent course is prevented. The patient, to be successfully treated, must come under observation early. The treatment consists of the subcutaneous injection of about 2 grams of an emulsion of a rabbit's spinal cord which has been dried in a sterile bottle over caustic potash for from seven to ten days. The beginning dose is not increased in size, but each day the emulsion injected is made from a rabbit's spinal cord that has not been so long dried, until, when the twenty-fifth day of treatment is reached, the patient received 2 grams of emulsion of rabbit's spinal cord dried only three days and is considered immune or cured.

This, in brief, is the theory and practice of Pasteur's system of treating hydrophobia. It is entirely in keeping with the ideas of the present time. When we remember that the first application of the method to human medicine was made October 26, 1885, six years before the time we began to understand the production and use of antitoxins, it becomes one of the most remarkable achievements of medicine.

Frantzius (Centralbl. f. Bakt. u Parasitenk, May 12, 1898, xxii, No. 18) has studied the bile of animals immunized against rabies, and found it possessed of marked neutralizing effect upon rabies poison, so that when 0.2 gram of bile and 0.2 gram of comminuted rabid rabbit's medulla are simultaneously introduced beneath the dura of a healthy rabbit, no disease occurs. The bile of healthy oxen, sheep, hogs, etc., was also studied, but found it to be without effect. He concludes that the bile is the most powerful rabies antitoxin (?) yet discovered.

The action of the bile in this combination probably corresponds with that discovered by Koch, who found that the bile of cattle suffering from the Rinderpest or South African plague, exerted an immunizing power by which healthy animals could be protected from the disease.

Hogyes, of Budapest (Acad. des. Sci. de Buda-Pest, Oct. 17, 1897; Centralbl. f. Bakt. u. Parasitenk, 1887, ii, 579) believes that Pasteur was mistaken in supposing that the drying was of importance in attenuating the virus, and thinks that dilution is the chief factor. He makes emulsions of rabbit's medulla (1 gram of medulla to 10 c.c. of sterile broth) as a stock solution, to be prepared freshly every day, and uses it for treatment, the first dilution being 1:10,000; then on succeeding days 1:8000, 1:6000, 1:5000, 1:2000, 1:1000, 1:500, 1:250,

1:200, 1:100; and finally the full strength, 1:10.

Cabot (Jour. of Exp. Med. 1899, vol. iv, No. 2) prepared a stock solution of 8 parts of rabbit's brain and 80 parts of glycerine and water. The quantity of glycerine added comprised one-fifth of the total bulk. After the emulsion was made it was filtered through sterile cheese-cloth. This emulsion containing the glycerine, if kept in the ice-chest, will be of standard virulence during the entire period of immunization. As the results of his experiments, Cabot found the dilution method attended with danger to the animal immunized, which is not true of the dried-cord method of Pasteur. The latter method is therefore the one to be preferred.

If an accurate diagnosis of rabies can be made, in cases where animals thought to be mad and have bitten human beings, by a simple histologic examination, much time can be saved in beginning the Pasteur treatment and probably an increased number of cases saved.

Anti-Rabic Serum.—The serum of animals that have received repeated injections of the crushed nervous tissue of rabid animals is neutralizing or destructive to the rabies virus in vitro, and is called anti-rabic. It was first mentioned by Babes and Lepp (Ann. de l'Inst. Pasteur, 1889, iii), who thought it exerted a depressive power upon other animals. Marie (Compt. rendu Soc. Biol. t, lvi, June 18, 1904, p. 1030) finds that this reaction is specific as

simple neurotoxic serum—i. e., serum of an animal given repeated injections of crushed normal nervous tissue—is inert in its action upon the virus. The activity of the anti-rabic serum is also found to be in proportion to the virulence of the virus and quantity of the virus introduced into the experimental animal.

CHAPTER XIV.

Tuberculins.

Relative to the various sorts of tuberculins, the following is quoted from Working Bulletin No. 1:

Bacillen Tuberculin ("B E").—This is prepared by triturating or grinding the bacilli and suspending the same in normal salt solution. The germs are killed by this operation. The operation of grinding requires about two weeks. As there is still possible danger of living germs existing in the suspension. Bacillen Emulsion is usually rendered safe by the additional process of heating the suspension for about one hour at 60° C. In either case it is preserved by $\frac{1}{2}$ to 1 per cent. phenol or lysol. It therefore differs from a bacterin only in the fact that it is prepared from ground bacilli instead of whole bacilli. However, to all intents and purposes it is a bacterin.

Tuberculin Rückstand ("T R") or New Tuberculin.—Koch in 1897 described the preparation now known as Old Tuberculin, which he called "new" to distinguish it from his first introduction. "T R" is also prepared from ground bacilli but differs from Bacillen Emul-

sion in method of preparation. The ground bacilli are treated with physiological salt solution, centrifugated and the supernatant opalescent fluid discarded, and the residue from this dried, ground, treated with physiological salt solution, centrifugated, and the clear supernatant fluid collected and retained. This process is repeated until all the residue is taken up. The clear centrifugates are united and preserved by treating with glycerin to 20 per cent. This product is standardized so that 1 c.c. represents the active substances found in 10 mg. of the dried bacilli.

Old Tuberculin ("O T").—This product is a glycerin extract of tubercle germs, and contains all of the soluble secretion products of the tubercle bacilli, in a 50 per cent. glycerin solution. It is prepared from pure cultures of the tubercle bacilli of five or six weeks' growth upon five per cent. glycerine bouillon. The culture medium containing the germs is evaporated by heat to 1/10 of its volume and filtered through porcelain to remove the germ bodies.

Tuberculin Denys (Bouillon Filtrate) ("B F").—This product consists of the filtrate from bouillon cultures of the tubercle bacillus and contains all the soluble products elaborated by the bacteria while grown on bouillon. It differs essentially from Old Tuberculin in that no heat is used in its preparation and that it is not concentrated.

Relative to the infections due to the *Bacillus Tuberculosis* and the application of the

Tuberculins the following is quoted from Allen's "Vaccine Therapy and Opsonic Treatment, Fourth Edition, 1913":

Nature of Infection.—Sufficient evidence has now been accumulated to convince most minds that are open to conviction that the human and bovine strains of the tubercle bacillus are distinct, though closely related, types. Just, however, as there are intermediaries between the *B. typhosus* and *B. coli*, so there are intermediaries between the human and bovine types of the tubercle bacillus; but these are only rarely encountered. While infection by the bovine type is quite common in young children, it becomes less and less common with advancing years, and I think it must be admitted that Spengler was wrong in attributing a very considerable percentage of cases of pulmonary tuberculosis to infection by the bovine type either alone or in conjunction with the human strain. Bovine pulmonary tuberculosis in adults would appear to occur in less than 5 per cent. of all cases of phthisis. None the less there are certain definite advantages derived from employing highly polyvalent tuberculins, derived from both human and bovine strains, in the treatment of this disease, and this procedure is the best alternative to the preparation and use of autogenous tuberculin.

Diagnosis of Tuberculosis.—In the early diagnosis of tuberculosis lies the best chance of effecting a complete cure. To facilitate this

end numerous means have been devised, but it is quite impossible here to enter into a discussion on this point. Various clinical methods and observations may be employed, the help of X-rays sought, and such reactions utilized as those devised by Calmette and Wolff-Eisner, von Pirquet, Moro and Carle Woodcock. Here I propose to describe two methods only— one a comparatively new chemical method, which I have found to be of decided help in doubtful cases, the albumin test of Rogers; the other, the oldest test of all, viz., the diagnostic use of Old Tuberculin which I agree with Bandelier and Roepke, Moeller, Fremuth, and others in regarding as perfectly safe when properly employed, and as giving by far the most reliable results of all.

Roger's Albumin Test is performed as follows: To 5 c.c. of the sputum 20 c.c. of normal salt solution and 5 or 6 drops of strong acetic acid are added. The mixture is well shaken and filtered and the filtrate tested for albumin by any of the usual ways—i. e., by boiling, the addition of nitric acid, potassium ferrocyanide, or trichloroacetic acid. If the result is doubtful, a fresh portion of filtrate should be further diluted with 1 or 2 parts of the salt solution, and again tested. In order to secure reliable results the sputum must be fresh, and the inclusion of saliva avoided as much as possible. Rogers, Buitron, Veresci and Lesieur, and Privéy have carefully observed the results given by this test, and have found: (1) that of cases

without physical signs, which subsequently proved to be tuberculous, at least 75 per cent. gave a positive reaction; (2) that in all cases with tubercle bacilli in the sputum the result was positive; (3) that in miliary tuberculosis and pleurisy the result was not constant; (4) that cases of acute lobar pneumonia reacted, and that when the reaction persisted into convalescence a new focus or a complication was indicated. Acute broncho-pneumonia and acute pulmonary edema were also positive. On the other hand, in acute bronchitis it was usually negative, in chronic bronchitis and in emphysema always so. In cardio-renal cases a positive reaction was often seen.

A positive reaction, therefore, indicated a pulmonary origin of the exudate, and excludes a bronchial source, and the more marked and constant the result the greater the likelihood of phthisis or pneumonia.

My personal experience of the test is not extensive, but this I can say, that in the few cases of doubtful pulmonary tuberculosis where physical signs were almost absent, and tubercle bacilli not present in the sputum, and a positive reaction was given to the albumin test, subsequent events confirmed the accuracy of the deduction in each instance.

The Old Tuberculin Test.—If a healthy individual receive an injection even so large as 0.01 c.c. of Old Tuberculin (Koch), no symptoms beyond slight local tenderness will be exhibited. The case is very different with a person

afflicted with tuberculosis, especially if in an early stage. If the dose of tuberculin be extremely small, no effect may be noted; if larger, a local hyperemia of the infected area; if still larger, a congestion; while if larger still, a constitutional disturbance of varying degrees of severity will result. If the infected areas be visible, as in the larynx or pharynx, the hyperemia and congestion can be readily detected. In the lung there is an increase in the symptoms, confined to the area of infection; the auscultatory signs are magnified and resemble a catarrhal condition of greater degree. Fine rales may appear where none were to be found previously or their number may be increased. Careful charting of the signs before and during the reaction is therefore necessary.

It is possible to have this local reaction without any general one. If the latter be present, a few hours after the administration of a small dose of tuberculin the patient begins to feel a little nervous or tired, and perhaps has a heavy feeling about the limbs. With this there may be a slight rise of temperature of a fraction of a degree or a slightly accelerated pulse. With a larger dose the tired feeling and heaviness of the limbs becomes a true ache, which extends to the back and head, and the feeling is that of an on coming cold. With this the temperature usually rises one or two degrees, and the patient may develop a cough where none was present before. If the dose be still larger, the

patient may have a rigor, and nausea and vomiting occur.

The more experienced the physician, the less the amount of general reaction that he requires to establish a diagnosis, and an endeavor is made so to adjust the dose that a rise, at all events, of not more than 1° F. shall occur in temperature. If this be already above 100° F., the use of the test is contra-indicated, at all events, until rest and other appropriate means have reduced the temperature to the region of normal.

Inasmuch as the reaction usually shows itself in from eight to twenty hours, the dose of tuberculin is best given at eight or nine o'clock at night, the temperature being then taken at six o'clock next morning and at two-hourly intervals. Examination of the chest for the local reaction should begin at the same time, and be repeated at three to four-hourly intervals until the presence or absence of local reaction is established. For the purpose of the test Koch's Old Tuberculin is usually employed. Some people being very sensitive to it, it is best to begin with a dose of only 0.0001 c.c., to which only very exceptionally is any response made. Should no reaction occur, the dose is increased; 0.001, 0.003, 0.005, 0.007, 0.01, 0.1 c.c. being used at successive intervals of two or three days until a positive result is secured, as is usually the case with the second or third of these doses in tuberculous cases. A negative result with the last of these doses is considered

to be final so far as infection by the human type is concerned. If thought desirable, infection by the bovine type may be excluded by repetition of the test with bovine Old Tuberculin (P. T.). Some cases of advanced phthisis do not respond to the test, but these present little difficulty in diagnosis. It has also been stated that certain cases of syphilis have given a positive reaction, but against this it must be borne in mind that sufficient proof that these cases were not also infected somewhere by the tubercle bacillus has not been always forthcoming.

Contra-indications to use of the test are: (1) If the temperature rises above 98.6° in the axilla, or 99° F. in the mouth; (2) if definite signs of tuberculosis be present, if tubercle bacilli be present in the sputum, or if there has been a recent attack of hemoptysis; (3) if there be grave renal or cardiac trouble; (4) if the patient be subject to epileptic fits.

Immunity against the Tubercle Bacillus and the Tuberculin Reaction.—One attack of tuberculosis does not seem to confer any immunity against another, but, on the contrary, rather to predispose to it—that is, if we except the immunity to subsequent infection by the human strain which appears to be conferred by an infection by the bovine strain. That general constitutional immunity, due probably to biochemical causes, exists is highly probable, but local immunity appears to be a most important defensive mechanism.

Phagocytosis apparently is a most important agency in the destruction of the bacilli, and is carried out almost entirely by the giant and endothelial cells. Whether the polymorphonuclear leucocytes play any part therein, except perhaps in cases where the bacilli have gained access to the general circulation, is very doubtful. Opsonin, partly of the thermostable variety, but chiefly of the thermolabile, can be demonstrated in the blood-serum; but whether sensitization thereby of the bacilli is necessary prior to phagocytosis by the giant and endothelial cells has not been determined.

Wasserman and others have demonstrated the presence of antibodies in those who have been immunized with tuberculin; no bactericidin or antitoxin has been demonstrated. Lysin and agglutinin are frequently present, but are sometimes absent even in cases that are doing well.

The Tuberculin Reaction.—The exact manner in which the tissues of the tuberculosis subject react to an inoculation of tuberculin has been the source of much argument, and the matter of much investigation. The chief cause of dispute has been the delay which occurs in the response to the inoculation, a delay in no wise peculiar to tuberculin, but which is likewise experienced when any other vaccine is employed.

The recent work of Wasserman, Wolff-Eisner, Rosenau, Vaughan and Wheeler, and of others, has tended to show that in the tuber-

culous individual the cells are sensitized by the action of the infecting bacillus and its products, and that when tuberculin is injected it is split into a toxic and a non-toxic portion, the former of these being rapidly bound by the sensitized cells and giving rise to the tuberculin reaction. In non-tuberculous individuals the condition of hypersensitiveness of the cells does not exist; when tuberculin is introduced into the tissues the splitting process into the two constituents is slow, the combination of cell and toxin either does not occur at all, or only to a slight extent, and the toxin is rapidly destroyed or discharged. When hypersensitiveness exists certain changes are produced in the cells whereby they are enabled to break up the tuberculin and combine it with great rapidity.

Meyer and Schmitz have attempted to determine what the substance is that reacts with the tuberculin. They infected rabbits with bovine tuberculosis, bled them, and allowed the serum to stand for twenty-four hours mixed with bovine bacilli, and then injected it into healthy animals; these became ill, with considerable rises of temperature and other constitutional disturbances. The serum from animals with advanced tuberculosis was found to answer best, and a still stronger reaction was obtained when washed blood corpuscles were used instead of serum. Also, when the washed blood cells of tuberculosis animals were allowed to react with tuberculin and saline solution, the

mixture centrifugalized, and the saline solution alone injected into healthy animals, a reaction was still obtained; this, however, was never the case when the blood cells or serum of healthy animals were employed. Heating above 65° C. did not destroy the bodies that gave rise to the reaction.

It would thus appear that in the blood of the infected individual there circulates a substance combined for the greater part with the red blood cells, which combines with tuberculin, and is then capable of producing a febrile reaction and other symptoms of disease in healthy subjects.

Choice of Cases for Tuberculin Treatment, Choice of Tuberculin, Control of Dosage and Intervals—Results.—The decision as to whether a given case of pulmonary tuberculosis is or is not suited for tuberculin treatment is a problem by no means devoid of difficulty. The chaotic state into which the minds of all were thrown in the first place by the failures and accidents encountered under the original system of dosage advocated by Koch, and in the second place by the disappointing results obtained by the application of Wright's principles to the dosage of tuberculin in cases of pulmonary phthisis, has done much to impede progress. The better understanding that has been recently attained of the nature of the tuberculin reaction and of the means whereby the body acquires immunity against the tuberculo-toxin on the one hand, and the bacilli themselves on

the other hand, is serving to explain why it is that the small and infrequent dosage, so well adapted to the treatment of strictly localized and surgical tuberculosis is ill-adapted to the widely diffuse pulmonary form. In the former variety autotoxemic disturbances are slight, and there is no necessity, therefore, to overcome sensitiveness, and establish a high degree of tolerance to the tuberculin toxin. In the latter condition, the autotoxemic disturbances, as evidenced by irregular pyrexia, quickened pulse-rate, and bad general conditions, are considerable; sensitiveness to the tuberculin toxin is then very high, and can be overcome only by establishing a high degree of tolerance by the administration of such doses of tuberculin as will rapidly nullify the administration from within of irregular dosages at irregular intervals. It is at the same time obvious that the difficulty of establishing a satisfactory degree of toxin immunity will be minimized by the adequate control of the inoculations of autotoxins, and that these latter may be so uncontrollable and so considerable as to render impossible the task of overwhelming their irregular impulses by the well-ordered waves of immunity set up in response to stimulation with regular and adequate doses of tuberculin. The slight discord introduced into the performance of a piece of music by a flautist in a band may easily be masked beneath the greater volume of harmony emitted by the brass, but not all the sweet tones of flute and

clarinet and harp will mask the blatant discords of trombone and double bass. Hence it is that phthisical cases in whom autoinoculation effects are marked are unsuited to tuberculin treatment and that the control of these by rigid rest and other measures becomes a matter of such urgency and importance.

The statement is frequently made that cases of mixed infection are unsuited to tuberculin treatment; this is a very misleading statement. That cases of mixed infection are unsuited as a rule to tuberculin treatment is due, not to the fact that they are cases of mixed infection, but to the fact that autoinoculation effects are as a rule marked, and that, moreover, it is almost impossible to separate the autoinoculation effects referable to the mixed infection from those referable to the tuberculous infection. The fact that mixed infection gives rise to increased cough and respiratory efforts has also to be borne in mind. These cases, therefore, are not intrinsically unsuited to tuberculin therapy; they are so only temporarily, and until the mixed infection has been dealt with adequately according to the methods outlined in an earlier part of this chapter. There is a third class of case in which tuberculin treatment appears to be contra-indicated; i. e., that class in which sensitiveness to tuberculo-toxin is so great and tolerance so low that the administration of doses of tuberculin sufficiently great to overcome these disabilities is rendered impossible by the grave constitutional disturb-

ances thereby engendered. To this it may be urged that it is only the treatment of such cases by massive doses of tuberculin that is contra-indicated, and that such cases are well suited to the small and infrequent dosages advocated by Wright. This may indeed be true, but in practice I have found it otherwise; small infrequent doses do nothing to diminish sensitiveness and increase tolerance to the tuberculin toxin, but have rather the contrary effect; and the better practice in these cases is probably to place them under the best possible conditions, and leave them to establish tolerance and diminish sensitiveness by means of controlled autoinoculations. This class of case is by no means common and it is to be expected most among the very early closed cases; occasionally such a condition is temporarily established by the administration of a diagnostic dose of tuberculin. Finally, in the following forms of the disease tuberculin treatment is liable to do more harm than good: (a) In the broncho-pneumonic form; (b) in those where caseation is marked, for softening, cavitation, and perhaps serious hemorrhage and dissemination may be induced; (c) in those where the disease is very wide-spread, especially if the pulse be very rapid—i. e., 120 or over—a very rapid pulse is a much stronger contra-indication than is a high temperature, for the latter is usually much easier of control than is the former; (d) serious complications. On the other hand, homoptysis, slight complications,

and pregnancy do not contra-indicate tuberculin treatment.

Choice of Tuberculin.—With the general view that all tuberculins produce the same effect, and act in a similar manner and that one preparation brings about as good results as any other, I cannot at all agree. While it is probably true that the use of each and every tuberculin tends to establish tolerance and diminish sensitiveness, it must surely be admitted that the use of such preparations as contain toxins only can never suffice to bring about an antibacterial immunity. Tolerance to tuberculo-toxin will enable the sufferer to go about his daily duties even though he continue to expectorate great numbers of bacilli and perhaps suffice to minimize greatly the ill-results which would otherwise inevitably attend the bacterial infection, but it can never lead to its extinction; this only a high antibacterial immunity can bring about. Granted that we know but little on this subject of antibacterial immunity, it may yet be reasonably deduced from analogy with every other variety of organism that the administration of the bacterial bodies and their essential protoplasm is the best available means for inducing its increase. When, therefore, toxemic symptoms predominate, it would appear to be most rational to endeavor to stimulate antitoxin formation by the administration of such toxic products as Old Tuberculin, P. T. O., or Bouillon Filtrate; in the more severe cases beginning with the mildest preparations

—viz., the P. T. O.—and concluding with the most potent the Old Tuberculin. In very sensitive cases, however, the use of the bacillary emulsion may, owing to its very slow absorption, possess distinct advantages. When, on the contrary, toxemic symptoms are in abeyance, it would appear to be more reasonable, perhaps after a preliminary course with a toxin preparation such as Old Tuberculin, to endeavor to establish a true anti-bacterial immunity with the aid of T. R. and bacillary emulsion. Whatever preparation is utilized, I feel sure that the autogenous preparation is necessarily the most suited to the case, and the ease with which the tubercle bacillus can now be isolated from the sputum will facilitate greatly the experimental confirmation of this view. In default of the autogenous tuberculin, a polyvalent stock preparation is next to be recommended, while the combination of human and bovine strains, which I first advocated three years ago, appears to possess distinct advantages.

The Control of Dosage and Interval.—(1) According to Wright's method; (2) according to Koch's method, modified according to more recent experiences.

1. In Wright's methods, as we have already seen, the object is to give a series of independent immunizing stimuli, whereby the general well-being is improved without any regard being paid to increase of tolerance or diminution of sensitiveness. If the method be con-

ducted in its entirety, the control of dosage and interval is by means of determinations of the opsonic index, the aim being to employ such doses as will induce the maximum use of index and will maintain it at a high level for the longest possible time, reinoculation being performed as soon as the decline of index sets in, and increment of dosage being made when the old dose no longer proves efficient in these directions. The initial dose of any tuberculin preparation usually employed in this method varies from 0.000001 c.c. to 0.00001 c.c., and only exceptionally is it finally raised above 0.00001 c.c. to 0.0005 c.c. The interval between the administrations varies from ten to fourteen days.

Occasionally the method is employed more empirically, the guidance of temperature chart, general condition, and past clinical experience, being substituted for that of index. As we have already seen, this system of small infrequent dosage is admirably adapted for the treatment of localized and surgical tuberculosis, but the general consensus of opinion now is that it is ill-adapted for the treatment of pulmonary tuberculosis and is accordingly being more and more discarded in favor of Koch's original method suitably modified.

2. The Method of Immunization According to Koch, Also Known as the Intensive Method.—In this method the aim is to train the tissues to be able to cope with such doses of tuberculo-toxin as are liberated from the infected foci

without evincing signs of pronounced constitutional disturbances. In order to achieve this end tuberculin is administered at short intervals in rapidly increasing doses, for this has been found to be the only way in which hypersensitiveness can be overcome and tolerance induced. The cure of the focal lesion is left to natural processes, these being merely stimulated to increased action by the hyperemic condition there induced by the inoculations.

Some authorities there are who endeavor to achieve the desired end by so adjusting their stimuli that constitutional disturbances are avoided completely is possible; others adjust their stimuli so as to produce such disturbances and regard them as evidences of efficient dosage; others, again, adjust their stimuli without any regard to the production or not of constitutional disturbances, aiming chiefly at being able to administer the highest possible dose of tuberculin in the shortest possible time. It is quite outside the scope of this work to go into these various methods; the one most in favor is that whereby the dosage is made the highest possible that will just avoid the production of marked constitutional disturbances. Whatever the preparation of tuberculin employed—and some prefer to employ Old Tuberculin throughout, others T. R., or B. E., or Beraneck's tuberculin throughout, while others, again, prefer to employ P. T. O. P. T., and Old Tuberculin in sequence—the initial dose is quite small. Thus, Denys and Wolff-Eisner begin with not more

than 0.000001 c.c., Aufrecht with 0.000025 c.c., Bandelier and Ropke with 0.000001 to 0.00001 c.c., Neumann with 0.000005 c.c., Krause with 0.00002 c.c., Moller with 0.000001 c.c., Bandelier and Ropke with 0.00002 to 0.0002 c.c., and Romisch with 0.0002 c.c. of T. R. or B. E. In three or four days the second dose is given, different authorities making different increments on the initial dose; thus making use of a double dose, but Bandelier and Ropke use one increased by half and Neumann makes an increment of one-third only. Thereafter different scales are employed; some use the progression, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30 and so on wherein there is a sudden marked increase after each series of ten inoculations; others use a progression such as 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 15, 20 and so on; while Bandelier and Ropke advise 1, 1.5, 2, 3, 5, 7, 10, 15, 20, etc. Whatever the notation employed for estimating the appropriate series of dosage, nearly all authorities who follow the system of avoiding reactions adopt the following principle when a reaction is produced; they wait till all signs of the reaction have passed off, which varies from three to seven days, and then begin again, either with the dose which last failed to produce a reaction or with one of half this amount and then increase as before.

As regards to final dosage which in the absence of a reaction thereto is regarded as demonstrating that a condition of full tolerance has been attained, authorities slightly differ;

1 c.c. of the undiluted tuberculin is the limit fixed by most, but 0.1 c.c. is regarded as sufficient by many. These latter, of whom Petruschky is one of the chief advocates, alternate periods of treatment for three months. After the maximum has been attained, the treatment is discontinued for three months and then begun again *ab initio*, three or four such courses being administered whenever possible.

All these authorities unite in disregarding reactions at the foci of disease and state that the dosage which will produce a general reaction is less than the dosage which will produce a focal reaction of such magnitude that it can be observed. In this I unhesitatingly state that they are in entire error. If sufficient care is taken to observe and record with accuracy the clinical signs in the chest before the administration of such a dose of tuberculin as will produce none but the slightest possible signs of general reaction, and these observations are continued at frequent intervals, such as six, twelve, twenty-four and forty-eight hours, after the inoculations, I am certain that in all but a very small percentage of cases marked changes in the physical signs can be detected, changes precisely similar in character, if less in degree, than those already described on pp. 399-406 (where the author gives consideration to the use of other vaccines in the treatment of mixed infections), as being produced in response to an inoculation with an efficient dosage of a vaccine of catarrhal or-

ganisms, or of one corresponding to the organisms constituting the mixed infection. I would maintain that herein lies by far the best, easiest and most reliable guidance to the appropriate dosage and intervals. Raised tolerance and diminished sensitiveness to tuberculo-toxin are desirable objectives, but they are not the real objective that we should have in mind. This is, firstly, the improvement of the general condition; secondly, the improvement of the focal condition; thirdly, the extinction of the infection, and that scheme of dosage is obviously the best which produces the greatest amelioration in the focal condition, all other things being equal. Surely it is only logical then, to claim that the best basis upon which to found a scheme of dosage is that built upon the changes produced at the foci of disease. It is on such lines that I now treat all my phthisical patients and the principle I have adopted is as follows: Begin with a very minute dose of that tuberculin which seems best adapted to the case. By a very minute dose I mean 0.00001 c.c. for apyrexial cases, and 0.000002 to 0.000005 c.c. for pyrexial cases. The effect of this inoculation is closely watched and recorded. If no reaction or improvement occurs within three days, the initial dose is repeated; if, again, no reaction or change within three days, double the initial dose is given and so on. Once a dose produces a focal reaction—and I have never yet seen a dosage which produced a general reaction fail to produce a focal one

also—close observation is kept upon the altered physical signs. It may be stated as an axiom that in a case capable of making improvement, any dosage which will within twenty-four hours produce a reaction at the foci of disease, as evidenced by apparent increase of the involved area, increased moisture of the sounds or multiplication of their number, will also, after a variable period—it may be one, two, three or more days—likewise induce a more than corresponding amelioration in the physical signs, so that there will be a time when the focal condition is better than it was before the inoculation was performed. After a further period—it may be of one, two three or more days—retrogression will begin and this is the signal for an immediate reinoculation. Under this system, which I would maintain is the most logical and scientific one yet devised, if unfortunately the one calling for the most care and attention on the part of the doctor, increase of dosage is indicated only by failure of production of an immunizing response at the focus of disease, and may be made according to the progression 1, 1.5, 2, 3, 5, 7, 10. Occasionally a focal reaction of the following type is produced. Instead of increase in the area of apparent involvement and of the moisture of the sounds, there is a diminution in these directions within twelve to twenty-four hours, either with or without the production of a slight general reaction. This is to be regarded as indication of a minimal effi-

cient dosage, and of the advisability of an increase being made therein at the next administration.

Only very rarely, indeed, have I found a dosage produce a general reaction, and at the same time fail to produce a focal one. On one occasion a change to B. E. from Old Tuberculin overcame the difficulty; on another occasion I could find no scheme of dosage that would suit the patient. I found it impossible to increase the dose of Old Tuberculin beyond 0.00002 c.c. without giving rise to marked general reaction and considerable constitutional upset, and decided that it would be wise to discontinue tuberculin treatment for a time and then recommence with 0.000001 c.c. B. E.

The one thing above all which should always be borne in mind is that whenever the system to which one may incline, whatever the scheme marked out for the treatment of any case, the man remains the prime consideration and not the scheme, and that when events are not taking the desired course, the one thing to do is to reconsider the case minutely and endeavor to learn in what essential particulars modifications may be required.

Autoinoculation in Phthisis.—To Marcus Paterson is entirely due the credit of demonstrating the great value of the autoinoculation method of treatment in pulmonary tuberculosis and to those who are interested in the method and would learn how to apply it and what it

can achieve, I would advise the perusal of this comprehensive monograph on the subject.

The facts bearing on the method are as follows:

1. That the irregular pyreias of pulmonary tuberculosis are due to excessive and ill-ordered autoinoculations with tuberculo-toxin derived from the infected foci.

2. That these can often only be controlled by the most absolute or so-called "typhoid" rest.

3. That the reparative processes and the acquirement of a high degree of tolerance to tuberculo-toxin may be greatly assisted by the induction of carefully ordered autoinoculation by means of graduated exercise and labor these autoinoculations being induced after adequate control of their spontaneous production has been gained if necessary, by the application of absolute rest.

That the method is one of extreme value may be at once admitted, but it has its disadvantages, among which are mentioned:

1. It can only be carried out thoroughly in institutions where the patients are well under control and where facilities exist for the provision of labor of various kinds and various grades.

2. That, strictly, it is only applicable to cases from which mixed infection is absent, for just as autoinoculation is induced with tuberculo-toxin, so autoinoculation is induced with the products of mixed infection and no means

are available of ascertaining how much of the autoinoculatory effects, which are measured by means of the temperature and pulse charts, are due to the tuberculo-toxin and how much to the latter toxins.

3. That whereas at the beginning of treatment, when the induction of only small autoinoculations is required, a practically unlimited amount of autoinoculation can be induced, as the case proceeds to "arrest" of the infective process and the tissues require large stimuli to produce immunizing effects, small stimuli only are capable of production. Paterson's contention is that if signs of autointoxication cannot be induced by a day's hard manual labor, there can be little danger in allowing such a patient to return to his occupation. This would be true were it the case that extinction of the infection and impossibility of producing autoinoculation effects were synonymous; this, unfortunately, is not the case, and the return of such an individual to hard work in unfavorable surroundings is extremely apt to lead to speedy relapse. It is somewhat unfortunate that Paterson should be prepared to regard the disease as arrested in an individual who continues to expectorate tubercle bacilli.

Personally, I think that there is a great field for the application of the valuable lessons which Paterson has learned and teaches. There is no tuberculin so well adapted to the treatment of a case as that formed by the affected

individual for himself, but I think the wisest procedure would be as follows:

1. Control autoinoculations by rest, absolute if required.
2. Eliminate mixed infections by means of autogenous vaccines.
3. Raise tolerance by a short course of Old Tuberculin.
4. Proceed to autoinoculate by means of graduated exercise and work.
5. When these stimuli fail to produce any reaction, recommence tuberculin treatment, perhaps best with the bacillary emulsion; employ the intensive method, and proceed to massive doses, and so endeavor to raise antibacterial as well as antitoxic immunity and eliminate the bacterial infection.

This elaborate method might well prove to be the best yet devised for the treatment of pulmonary tuberculosis.

Citron in his "Immunity." 1912, p. 61, gives the following suggestions as to the technical details of treatment of tuberculosis by inoculations:

1. The inoculation should, if possible, be given in the morning hours, for a restless night usually follows an injection in the evening.
2. It is best to so arrange the dilutions that the patient receives a fraction of 1 c.cm. at each injection.
3. The site of injections should be alternated between the back and breast.

4. The temperature should be taken every two or three hours and a chart of the same kept.

5. Disturbances in the general condition of the patient without the presence of fever are to be considered in the light of general reactions just as fever without other disturbances.

6. The patient's weight should be taken regularly every week and then the dose should be increased provided no loss in weight has taken place.

7. In cases where the pulse increases in rate or becomes poorer in quality, the treatment should be undertaken very carefully and the pulse constantly kept as a guide. Slowness of pulse can, as a rule, be considered a *signum bonum*.

Other Serums and Bacterins.—In the foregoing pages have been mentioned only those agents more commonly in use at this time; those of proven value. It is very probable, in light of the rapid strides being made in these lines, that this work will become antiquated and that very shortly, through the discovery and application of other products of this sort. It is likewise probable that many of the serums and vaccines, now being employed, will be put to greater use in time to come. While this little book is supposed to deal only with the hypodermic syringe, we have purposely given more than a little space to the consideration of biologic preparations, believing, in so doing, that we add to the value of the work thereby.

CHAPTER XV.

Anesthesia.

General Anesthesia.—That the hypodermic syringe is a useful adjunct in connection with general anesthesia has been evidenced time and again. In many cases of emergency, following accident, we find a marked shock, and through being able to apply either supporting agents in such a way as to be assured of prompt and efficient action, many lives have undoubtedly been saved. In those accidents, wherein many are injured, the hypodermic syringe plays an important role. With the introduction of hyoscine and morphine, or scopolamine and morphine, it became possible for the surgeon to place those whom he could not give immediate attention at rest, and it has been found that, after the injection of either of these combinations the patients were in better condition to receive the volatile anesthetic agent. If there was collapse, with or without internal hemorrhage, either of these combinations or atropine in full dosage, hypodermically, brought about a marked change for the better in the patient. The pulse which had been small, rapid and light previously, showed improvement and the

surfaces became more nearly normal, with the disappearance of the cold, clammy skin. Strychnine, likewise hypodermically, acted to increase the general tone and to restore the conditions to the normal. If there was a large loss of blood, infusion, either subcutaneously or intravenously, of normal salt solution, have been available through the hypodermic method.

For a number of years, some five or six decades, it has been the habit to induce general anesthesia through the use of chloroform, ether, ethyl chloride and ethyl bromide, as volatile agents and nitrous oxide. Recently, within the past decade, with the recognition of the deep slumber produced by either hyoscyne or scopolamine, in combination with morphine, it was proposed that the volatile drugs be omitted and that the obtunding effect be produced with the hypodermic use of either of these combinations. There are numerous reports of cases in which these combinations worked well but it was found that it was not possible to invariably keep the patient fully anesthetized with their use. Furthermore, in certain procedures, where absolute muscular relaxation was desirable, this latter condition did not invariably occur. This was particularly true in operations involving the abdomen. With the recognition of this fact, further attempts to employ either of these combinations, to the exclusion of the volatile anesthetics, were discontinued. However, despite the fact that hyoscyne and morphine or scopolamine and morphine were not

absolutely satisfactory alone, it was found that the use of either, prior to the administration of either chloroform or ether, better prepared the patient for the volatile drug and that he went to the scene of operation in a peaceful state of mind which very largely overcame the usual tendency to either operative or post-operative shock. In fact, those who were thus prepared, showed but little difference in general condition either prior or subsequent to operation. This fact being recognized, it has become the routine habit for a very large number of surgeons and anesthetists to employ these obtunding drugs, hypodermically, prior to exhibition of the volatile anesthetics.

The technic employed is extremely simple. Having prepared the patient for operation in the general way (excepting in emergencies, where prior preparation is usually impossible), two hours prior to the time of going onto the table, a subcutaneous injection of hyoscyne or scopolamine 1/100 grain and morphine $\frac{1}{4}$ grain is administered. If the patient is not quiet, or sleeping at the end of an hour, a second half dose is administered. As a rule the single dose is sufficient to both quiet the patient and allay his fears, both of the operation and the volatile anesthetic. In emergencies, where shock has followed accidental injury, either of these combinations will place the patient at rest, and that quickly in the general run of cases. Not only do these combinations act in the manner above mentioned, but they seem to overcome

many of the unpleasant features usually associated with the use of the volatile drugs, especially chloroform and ether. Not as much of either of the latter is required as when they are administered without such prior preparation. The first stage of anesthesia is decreased to a marked extent, and the stage of excitement is practically or wholly overcome and in many extensive operations the patient has been held under the volatile agent over a considerable time with less of the anesthetic than had previously been required to bring him under its influence initially. This lessening of either chloroform or ether practically does away with the general drug effects which at times follow in the wake of these agents, as the patient is not overdosed. The nausea and vomiting, subsequent to anesthesia, are as a rule, reduced or wholly obliterated. Not only do these obtunding drugs place the patient in better condition to receive the volatile agents, but subsequent to operation he is, almost invariably, assured of several hours of peaceful sleep, from which he awakes refreshed and better able to contend with the conditions usually following operative procedure. Not only does he awake within his own room and bed, and away from the usual horrors of the operating theater, but as a rule his knowledge of post-operative procedures is absolutely nil. Prior to his awakening, proctocolysis, if indicated, has been done and he does not have to undergo this during his waking hours. In fact, when he comes from under

the anesthetic, it is with an assurance that he will pass the coming hours as nearly comfortable as is possible, all things considered. Hypodermoclysis is also practiced prior to the awakening of the patient and without pain or discomfort to him, it usually being concluded before he awakens.

In obstetrical work the hyoscine and morphine, or scopolamine and morphine, combinations are employed with good effect and it not infrequently happens that other obtunding or anesthetic agent becomes unnecessary. With the appearance of the pains, a half dose is administered hypodermically. This does not have any seeming effect upon the uterine contractions but does have a marked effect upon the associated pains in some instances wholly obliterating them. The patient usually sleeps between pains but with the coming contractions awakens and assists the obstetrician in the usual manner. In some instances it may be necessary to give either a full dose initially or a second half dose or to administer a few whiffs of chloroform. Although the woman may complain more or less pain at the time, she rarely has any subsequent memory thereof and in many cases it has been reported that the patient has awakened, asking "when will the baby be born," or "is it all over," or other query denoting the fact that she had no realization of pain. In event of lacerations, these may be repaired during the subsequent stage of

slumber and frequently without the use of a single drop of a volatile anesthetic.

In connection with general anesthesia, and to overcome operative or post-operative shock, Crile has given the hypodermic added value. To overcome shock arising from operation, he produces local anesthesia of the skin, as well as of the deeper tissues, through the injection of cocaine, novocaine, eucaine, stovaine or urea and quinine, thus blocking off the fields of operation, in so far as sensibility is concerned. Not only does this obtund the site of operation during the time of operation, but if urea and quinine are employed the anesthesia, locally, continues for some time after, thus giving the patient freedom from the usual post-operative pains in and about the wound. In patients so treated he reports that the tendency to shock has been practically wiped out. In amputations, the injection of novocaine into the larger nerve trunks, prior to severing, likewise reduces the tendency to shock.

Spinal anesthesia with injections of stovaine, tropacocaine and other obtunding drugs of the like nature, may be practiced prior to the use of the volatile anesthetics, thus reducing the amount of the latter employed. The technic of spinal anesthesia will be considered on another page.

With the use of either hyoscine and morphine or scopolamine and morphine for their general obtunding effect and one of the local anesthetics mentioned, at the site of operation,

the danger of shock is practically obliterated and the comfort of the patient is very greatly increased. The use of both should be routine practice.

Local Anesthesia.—It is probable that Sargent and Russell in their "Emergencies of General Practice," 2nd Edition, page 4, give as good a description of the technic of local anesthesia as is obtainable and the following is quoted from that authority:

Some operations of urgency are best done under local anesthesia, as for example, a strangulated hernia in a patient who, on account of age, shock, or some cardiac, pulmonary or other disease, is an unsuitable subject for a general anesthetic. Some abdominal operations, such as the relief of intestinal obstruction, may, under similar circumstances, be performed under local anesthesia. It is of special value in operating for empyema when the patient is very ill and the respiration greatly embarrassed.

Speaking of the local obtunding of external and other tissues, they speak as follows:

(a) **The Application of Cold.**—This method is almost restricted to the incision of subcutaneous abscesses. A fine spray of ether or ethyl chloride is directed upon the site of the proposed incision until the skin is literally frozen, when the cut can be made without any pain being felt. The objections to this method are the hardness of the tissue which has to be cut

through and the pain which is experienced as the cold passes off.

(b) **Local Application of Analgesic Drugs.**—The uncertainty and risks, attending the use of cocaine renders its employment undesirable particularly in the quantities in which it would be required for an operation of any magnitude. There are, however, other drugs, which while possessing sufficient analgesic properties, are almost if not quite free from toxicity even in comparatively large doses. They can, moreover, unlike cocaine, be sterilized by boiling. These drugs are eucaïne, stovaine, novocaine and tropacocaine. It is found that if epinephrin is used together with the analgesic drug, the effect is increased both in intensity and duration. A large number of different formulae have been recommended by various writers, and many preparations can be obtained commercially in sealed vials, sterilized and ready for use. One of the best is Professor Braun's solution, consisting of novocaine, 0.5 per cent. suprarenin borate, 0.00064 per cent. and sodium chloride, 0.9 per cent.

For an operation of any magnitude a dose of morphia of about $\frac{1}{4}$ grain should be given before the operation is begun. The patient should be prevented from seeing what is going on and his attention may be distracted by conversation during the operation.

These drugs may be employed in different ways, namely by (1) general infiltration of the field of operation, and (2) deliberate "block-

ing'' of the main sensory nerves by injection into or around them, not necessarily at the site of operation but also at a distance; for example, blocking the ulnar nerve at the wrist for an amputation of the little finger.

The anesthesia appears much more rapidly if the injection is made into the nerve trunk than when perineural infiltration is employed. C. M. Page is of the opinion that stronger solutions of the drugs do not act much more rapidly than dilute, though their effect is more persistent; that in fact the bulk of the solution is of more importance than its concentration. The application of a Martin's bandage above the site of operation in the case of the limbs, has the effect of prolonging the anesthesia by retarding the diffusion and absorption of the drug.

(1) **General Infiltration.**—A large hypodermic syringe provided with a specially long sharp needle should be used, though the ordinary pattern can quite well be made to serve in an emergency. The needle is thrust into the skin so as to lie in the deeper layers of the true skin and not in the subcutaneous tissue, along the line of the proposed incision, and the injection made during the withdrawal. This insures, if properly carried out, absence of pain during the division of the skin. As the deeper parts are reached they can be rendered insensitve by repeated applications of the solution, or by injection into the nerves. The actual time of the operation is thus unavoid-

ably lengthened, but this is a matter of little moment compared with the advantages which, in selected cases, the avoidance of a general anesthetic confers.

(2) **Intra- and Peri-Neural Injection.**—These methods involve a more accurate knowledge of topographical anatomy than the foregoing and in emergency work would apply chiefly to amputation. The principle has been applied to the operation of rib resection for empyema by C. M. Page (St. Thomas' Hos. Gaz. Dec. 1909), whose method is best described in his own words:

“Before the operation area is washed, a puncture is made on the vertebral side of the proposed incision, if possible to the outer side of the erector spinae. The needle is passed in at the level of the intercostal space above the rib to be resected, the point is first made to impinge on the surface of the upper rib of the space and is then made to pass downwards till it dips into the subcostal groove; 3-5 c.c. of the selected solution are here injected. Two further punctures are made in relation to the two ribs below this, and the same procedure repeated, i. e., including the rib to be resected. This effects a perineural infiltration of the intercostal nerves. Just before commencing the operation the skin itself in the line of incision is infiltrated. If about ten minutes have elapsed from the time of the first puncture, complete anesthesia of all the structures involved in subsequent manipulation will be pres-

ent, the entire insensitiveness of the periosteum, bone and pleura, being in marked contrast to the pain present in those cases where simple infiltration alone has been employed."

Quinine and urea hydrochloride, which salt has come into prominence of late in the United States, for the purpose of obtaining local anesthesia by infiltration, is not mentioned by Sargent and Russell. It has all of the advantages of the drugs above mentioned and in addition is practically harmless in so far as untoward systemic effects are concerned. It is employed in much the same manner as are the other local anesthetics. Merck gives the dose as from $1\frac{1}{2}$ to 8 grains in 50 per cent. aqueous solution. Recently much lower percentage solutions have been used; 1, 2, 3 and 4 per cent. solutions have been found as effective as the higher one suggested, and less liable to act as irritants, with possible abscess formation. Crile recommends this agent for the "blocking off" of the site of operation. The effects of this salt pass over a longer period than do those of any of the other drugs employed for the obtaining of local anesthesia and this one thing recommends it, especially in the obviation of post-operative pain and discomfort.

Again referring to Sargent and Russell is found the very complete description of spinal anesthesia and the technic of application thereof:

We are not concerned in this chapter with the merits or demerits of spinal anesthesia as

a rival of general anesthesia in routine work. But as a means of preventing shock in grave emergency operations this method undoubtedly has a place. When anesthesia is satisfactorily induced, the afferent impulses from the operative field are effectually prevented from reaching the sensorium; with general narcosis this effect is not produced unless the depth of anesthesia is far deeper than is necessary to abolish consciousness.

Against this very great advantage must be set the fact that the psychical factor of shock is not abolished as it is with general narcosis and this objection is increasingly greater in proportion to the patient's racial or individual sensitiveness. Crile has advocated the combined use of spinal and general anesthesia in certain cases. The former prevents shock-producing afferent impulses from reaching the central nervous system, whilst the latter, given in the small quantity necessary to abolish actual consciousness, does away with the shock-producing psychical factor. The hypodermic injection of morphia and scopolamine in addition to the spinal anesthesia has a similar effect. Our own experience of spinal anesthesia has not been encouraging, but from a small number of cases we are not entitled to speak dogmatically. Our conclusions are drawn in the main from two sources—a paper by C. M. Page dealing with a large number of reported cases as well as his own experience and papers

by H. Tyrrell Gray based upon his large personal experience of the method in children.

Page, in December, 1909, tabulated over 23,000 cases collected from various sources as follows:

Drug	No. of Cases	Fatal		Col-lapses	Oculo-motor Palsies	Rate of Mortality	
		A	B			A	Total
Cocaine	6,875	12	12	54	..	1 in 573	1 in 271
Tropacocaine	7,459	6	5	12	3	1 in 1243	1 in 675
Stovaine ...	6,234	7	1	16	24	1 in 890	1 in 670
Eucaïne	817	1	1 in 817	1 in 817
Novocaine ..	1,355	3	..	10	7	1 in 449	1 in 449
Alypin	414	3	1	5	..	1 in 138	1 in 103
Totals	23,154	32	20	97	34	1 in 722	1 in 444

A—Deaths attributed to the direct action of the drug.

B—Deaths occurring when some other condition sufficient of itself to produce death, was present.

Of these drugs stovaine, novocaine and tropacocaine are most frequently employed. The last named appears to be at once the safest and least efficient. Stovaine has the great disadvantage of being precipitated and rendered inert by certain chemicals, particularly alkaline fluids. If, then the instruments are boiled as is usually done, in water with soda added, the drug is precipitated. It is necessary to use plain water for sterilizing the syringe and everything that is used for the spinal operation.

Many different formulae are employed. H. P. Dean recommends: Stovaine, 0.1 grm; sodium chloride, 0.1 grm.; and distilled water, 1 grm. A. E. Baker uses 10 per cent. stovaine with glucose 5 per cent. and distilled water 85 per cent.

The following solution can be obtained commercially ready for use, in sealed phials, each containing three cubic centimetres:

Novocaine0.15 grm. (5 per cent)
Suprarenin0.000325 grm.

The dose of this fluid should be from 2 to 3 cubic centimetres, or 35 to 50 minims.

H. Tyrrell Gray (Lancet, June 11th, 1910) reported 300 personal cases in children, with one death and six failures to produce anaesthesia. He has shown conclusively that the method can be employed satisfactorily in children, the psychical element in the production of shock being almost or entirely absent. Many of the operations in this series were performed for conditions of extreme gravity and it appears certain that the abolition of shock and the absence of the toxic effects of a general anesthetic contributed in great measure to the brilliant results obtained in some of these cases, notably the recovery of a child only seven months of age after resection of an intussusception and anastomosis by H. A. T. Fairbank. In this connection one point of special interest is brought out by Gray, namely, that "so long as the anaesthesia is complete, surgical shock is altogether absent, but that when the effect of stovaine on the nerve roots begins to wear off and anaesthesia passes into analgesia, signs of shock begin to appear." It must not be supposed that spinal anaesthesia is devoid of danger, though doubtless with increasing familiar-

ity with its technique and improvements in the preparation of the drugs employed, these dangers will be obviated or minimized. Death has occurred from respiratory failure and bulbar paralysis from the drug reaching too high a level and from meningitis. Serious and alarming after-effects have been recorded many times, such as persistent vomiting, severe headache, rigors, collapse, respiratory difficulty and paralysis of the bladder followed by cystitis.

Technique.—An ordinary antitoxin syringe, provided with a specially long, sharp needle, may be used for the injection. If the patient is well enough, the sitting posture is the most convenient; if not, he should be lying upon one side with the back flexed as much as possible. The needle may be entered in the mid-line just above the spine of the fourth lumbar vertebra, which lies on a level with the highest point of the iliac crests and thrust forwards and a little upwards; or it may be entered half an inch to one side of the mid-line and thrust forward, inward and upward, so as to pass between the laminae of the third and fourth lumbar vertebrae. As soon as the needle has entered the spinal theca, cerebro-spinal fluid will flow from it. It is essential that a flow of cerebro-spinal fluid should occur before the injection is made, in order to be quite certain that the point of the needle is in the subdural space. The syringe should now be connected with the needle, some of the cerebro-spinal fluid allowed to mix with the solution in it and the injection per-

formed. The patient should immediately be placed in the recumbent position, with the shoulders somewhat raised so as to prevent the drug reaching a dangerously high level. As the drug takes effect there is first a feeling of numbness in the legs, followed by weakness and ultimately, after a few minutes, there will be complete analgesia and a varying degree of motor paralysis.

CHAPTER XVI.

Shock.

Shock and collapse, until very recently, have been considered one and the same, in so far as the initial cause might be concerned but Crile has determined the fact that they are not due to one and the same cause, consequently the treatment is not relatively the same in both. He has shown that collapse is due to centripetal influence from without upon the vasomotor centers, sufficiently severe as to inhibit their activity temporarily but allowing of their restoration of function promptly under indicated treatment. Severe loss of blood may occasion collapse as may something appealing strongly to the moral senses. Shock is due to ★ prolonged external stimulation, or repeated action of this sort and leaving a condition which does not respond immediately to the action of drugs and other agents employed for relief. In all cases of both collapse and shock, the nerve cells undergo change, according to Crile (Br. Med. Jour. Oct. 1, 1910). In the first mentioned condition this change may be slight and the cells may recover promptly, while in shock there may be complete obliteration or disin-

tegration of the nerve cells. In both conditions there is a lowering of the blood-pressure; in collapse the pressure may be restored easily as compared with shock, where restitution is based wholly upon the repair of the cells of the vaso-motor centers. Collapse then is really nothing more than a functional disorder and one in which the restoration of the normal is a matter of comparative ease, while shock becomes an organic condition in which time is required as well as remedial agents in the bringing about of the normal.

Quoting from "Emergencies of General Practice," 2nd Edition, Sargent and Russell, is given a very clear idea of the clinical symptoms of shock:

The pulse is easily compressible, of small volume, rapid and sometimes irregular. The pressure may be estimated roughly by the feeling of the pulse but is more accurately determined by some form of sphygmomanometer such as that of Riva Rocci. In old people the rigidity of the arteries may give a false impression of the blood-pressure and must be allowed for, lest the patient be assumed to be in better condition than he really is. Other important symptoms are rapid, shallow and often irregular respiration, depressed mentation, general muscular weakness, lowered temperature, diminution or suppression of urine, sweating and an expression of a more or less characteristic kind, in which the face is pallid and pinched and the eyes sunken.

In consideration of the prevention of shock the same authors offer the following:

The precautions to be taken against shock as well as the measures to be adopted in its treatment, depend upon a clear conception of its causation, as well as its pathological anatomy.

Crile has shown that the above-mentioned cell changes are caused by (a) severe and repeated afferent impulses whether sensory in the ordinary meaning or not, e. g., from manipulation of intestines, or section of a large nerve trunk whilst the patient is under an anesthetic; (b) psychical influences, particularly fear; (c) loss of blood; (d) toxemia, either from bacterial toxins or drugs (ether and chloroform).

In emergency work one or more of the above-mentioned factors are likely to be already present when the practitioner first sees the patient; the psychical influence and loss of blood in a severe injury; e. g., a cut throat; the alarm, pain, irritation of the peritoneum and toxic absorption in a healthy patient suddenly seized with perforative appendicitis. In these cases not only has the shock already present to be treated, but all available measures must be taken to prevent additional shock during the operation.

The psychical element can be minimized by allaying the patient's fears, by preventing him from seeing or hearing the preparations for operation, and also by the hypodermic injection of morphia and scopolamine (hyoscine hydrobromide) gr. 1-200 to 1-100. Loss of

blood must be guarded against on ordinary surgical lines. The effect of afferent impulses can be minimized by gentleness of manipulation and in the case of amputation by injecting novocaine into the large nerve trunks before dividing them. In suitable cases spinal anesthesia may be used, in conjunction with minimal dose of chloroform, as a means of preventing shock in major operations upon the lower part of the body.

In their attention to the treatment of shock, other than through proper anesthesia, these authors show the worth of hypodermic medication very clearly as follows:

Treatment of Shock.

This consists essentially in adopting all the means available for raising the lowered blood-pressure. Naturally one first thinks of the rapidly diffusible stimulants, ether, alcohol and strychnine but too often their action is only analagous to whipping the tired horse; there may be a momentary response, only to be followed by a further fall and this is especially the case with alcohol and ether. The essential point is that the vaso-motor mechanism should be stimulated peripherally and not centrally; the blood-pressure must be raised and kept raised until the central vaso-motor mechanism has had time to recover. The means to this end are as follows:

1. Drugs.—Adrenalin raises the blood-pressure by its action upon the peripheral ateri-

oles. It may be given by hypodermic injection (5 minims of the 1 in 1,000 solution of adrenalin chloride) or better, by intravenous injection of saline solution containing 10 minims of the 1 in 1,000 solution in 2 pints of fluid. In this form it is best given by the continuous or intermittent subcutaneous method, because by this means it is possible to continue the peripheral effect of the drug over longer periods, and in accordance with the requirements of the case as indicated by the blood-pressure. The effect of adrenalin is very transitory, its properties being rapidly lost in the tissues. It is, for this purpose, quite useless to give by the mouth. Hemisine is a commercial product containing the active principle of medulla of the suprarenal gland. Its action is that of adrenalin and it may be given by the mouth (5 to 15 minims of the 1 in 1,000 solution) or hypodermically (1 in 100,000).

Tyramine is an active principle derived from ergot and may be given either hypodermically or by the mouth for the purpose of raising the blood-pressure in shock, its action in this respect being similar to that of adrenalin. It has the advantage that its effect lasts much longer than that of adrenalin.

Preparations made from the posterior lobe of the pituitary gland have an effect similar to that of adrenalin and the effect lasts longer. These, when available, are used in preference to adrenalin when required for subcutaneous injection and the effect is stated to be better

when intramuscular injection is employed. One preparation is on the market as "vaporole pituitary extract" and is supplied in sealed glass phials, each containing 1 c.c. representing 3 grains of fresh posterior lobe of the pituitary body. The dose is $\frac{1}{2}$ to 1 c.c. Another preparation which can be obtained in sealed phials ready for use is known as Pituitarian. Each phial contains 15 minims of fluid, equivalent to 3 grains of fresh posterior lobe of pituitary body, the amount suitable for a hypodermic or intramuscular injection. A third similar preparation is sold under the name of Pituitrin, of which 1 c.c. (17 minims) represents 1.5 grains of the fresh posterior lobe.

2. Saline Infusion.—By running normal saline solution directly into the venous system or by its more gradual absorption from the rectum or subcutaneous tissues, the blood-pressure can be raised, but the effect is very transitory and the fluid is rapidly removed by the skin and kidneys. When given slowly and in combination with adrenalin the effect can be prolonged considerably.

The fluid to be used is sterilized normal saline solution, which can readily be made by dissolving a drachm of common salt in each pint of water. When, in case of emergency, common salt has to be used, the solution should be filtered through a piece of sterilized gauze or muslin in order to free it from hairs and other foreign matter. For rectal injection the fluid need not, of course, be sterilized, but for

the other methods sterilization must be carried out with the greatest care and throughout the operation the most scrupulous asepsis must be maintained.

Intravenous Infusion.—This is by far the most rapid and efficient way of introducing fluid into the circulation and the one most generally applicable. The apparatus required consists of a scalpel artery forceps, scissors, aneurysm needle, canula rubber tubing and funnel, thermometer, measuring glass, ligatures and sutures.

Operation.—The skin over the front of the elbow having been thoroughly cleansed, the largest vein visible (usually the median basilic) is exposed by an incision an inch in length. It may be necessary to tie a bandage round the upper arm in order to render the veins sufficiently visible; it need hardly be said that the bandage must be removed as soon as the canula is in place. By means of the aneurysm needle two silk ligatures are passed beneath the exposed vein, about an inch apart; the lower one is tied and the upper one left loose. The funnel, the tube and canula, all previously sterilized with scrupulous care, are then completely filled with the saline solution at 105° F. (to which a little brandy, if thought necessary, may be added) so as to exclude all bubbles of air. A small oblique incision is made into the vein and the canula introduced in an upward direction. The upper of the two ligatures, which had been left loose is tied with a

single hitch so as to hold the canula in place. The fluid is now allowed to flow into the vein, the funnel being elevated as high as may be necessary to cause it to flow with moderate rapidity. This height is subject to great variation, a free flow being sometimes obtained with an elevation of a couple of feet, whilst at other times the funnel must be raised three or four feet. When sufficient fluid has been introduced the canula is withdrawn, the ligature tied tightly and the wound closed.

When the case is very urgent, the operation may be shortened by introducing a large anti-toxin needle directly into a vein, stabbing through the skin and vein wall in the direction of the heart and attaching the tube and funnel to the needle.

In cases of severe hemorrhage it is often advisable to add to the normal saline solution a small quantity of adrenalin chloride, 10 minims of the 1 in 1,000 solution in 2 pints of saline. If more than 2 pints of fluid is necessary, the additional quantity should contain no adrenalin. The amount to be introduced is to be estimated by the effect upon the pulse. When saline alone is used, however much infused, the blood-pressure is only very temporarily raised above the normal. After an infusion sweating is sometimes most profuse and the amount of urine passed may be enormous. An undoubted danger attending the introduction of an excessive quantity of fluid directly into the circula-

tion is oedema of the lungs, from which death occasionally occurs.

Rectal infusion is likewise employed in the treatment of shock, but as this is without the bounds of the subjects considered within these pages, it will not be discussed. Sargent and Russell give this portion of the treatment thorough consideration. Again quoting from their work we obtain the following:

Subcutaneous Infusion.—Saline solution can be absorbed with fair rapidity from the subcutaneous tissues and this is a method particularly adaptable for children. It is best given by the continuous method as follows: one or more large hypodermic needles are connected by means of a long piece of rubber tubing with a vessel containing the saline solution. Everything must be sterilized and the whole procedure conducted with the most scrupulous regard for asepsis. The needles are thrust into the subcutaneous tissue of the flank or chest wall and the vessel is suspended above the bed at such a height as to ensure the liquid being forced slowly into the subcutaneous tissue. It may be necessary to alter the position of the needle if a very tense swelling is produced. The temperature of the fluid must be kept constantly at 105° F. In this manner a pint or more can be introduced in the space of an hour but it is a tedious and sometimes painful method and requires the undivided attention of a nurse.

Intraperitoneal Infusion.—In abdominal operations saline solution may be left in the peritoneal cavity from which it is rapidly absorbed into the circulation but the amount which can be introduced in this manner is not large and the method is obviously capable of but limited application.

CHAPTER XVII.

Syphilis.

With the discovery of the cacodylates and later of arsenobenzol, the advantages of the hypodermic treatment of syphilis was emphasized. A few adventurous practitioners had employed mercury hypodermically for some time but this method had not come into prominent use until after the introduction of the above-mentioned agents. Today, however, we see a marked change in the methods of treatment and not only are the arsenic but the mercurial compounds, as well, administered in this manner.

During the earlier days of the hypodermic treatment of syphilis through the application of the mercurial salts it is very possible that some of the failures and disastrous results following were due to the use of insoluble salts of this metal, as it is pointed out by Schamberg that numerous deaths have followed in the wake of the use of such agents.

While it has been a recognized fact that the mercurials, in many cases, are followed by a cure of the disease, it has not always been followed by success. Not only has it shown failures but in addition, much time has been re-

quired to obtain permanent results through the use of the mercurials. As a rule not less than two years have been required to eradicate the disease under the use of mercury.

Arsenic has been known to be an antidote against syphilis for upwards of a century, as in 1810 G. N. Hill mentioned it in cases where mercury failed. However, it has only been within the past decade or two that it has been employed to any great extent, this probably being due partly to the fact that none of the known arsenicals gave the desired results without undesirable drug effects. Sodium cacodylate was the first arsenical compound to give anything like the desired results but it was not demonstrated that it invariably brought about a cure in all cases. Still later and within the past decade, Ehrlich introduced arsenobenzol, or what is better known "salvarsan," which gave phenomenal results in case after case. Despite these results, arsenobenzol, as time went on, was shown not to be invariably successful in the eradication of the disease and today we find this drug, combined with mercury, employed in the majority of cases. Salvarsan, as originally manufactured, required the services of a chemist whenever an injection of the drug was to be given as the placing of it in solution properly was such as to need a considerable technique. To overcome this, Ehrlich offered a more readily soluble salt, neosalvarsan; one requiring practically no assistance upon the part of the chemist and it is this

latter product which is in many instances, the more popular today.

The arsenic element of both salvarsan and sodium cacodylate is that which is the spirillicide and in so far as drug poisoning is concerned, it is contended that arsenobenzol presents no greater danger than do the mercurials. Wechselmann reports 4500 injections without a single case showing drug intoxication.

Atoxyl (sodium-amine-phenyl-arsenate) is another arsenic compound which is also employed, as is mercury cacodylate (mercury dimethyl arsenate), and in certain selected cases, in which there is anemia, iron cacodylate (iron di-methyl arsenate). None of these show drug intoxication if employed in proper dosage and under proper indications.

Among the mercurials which are employed are those already mentioned and in addition mercury benzoate, 1 c.c. of the solution of the salt in water representing $\frac{1}{8}$ grain of mercury as metal; mercury sozo-iodolate, 1 c.c. of a watery solution being equal to 1-12 grain of metallic mercury; mercury salicylate; gray oil, an emulsion of metallic mercury in an oil jelly and containing 1 grain of the metal per $\frac{1}{2}$ c.c.; mercury succinimide; mercury bichloride; as well as other of the soluble forms of salts of the metal as mentioned under the chapter devoted to mercurials.

With the introduction of the Wasserman test reaction in the diagnosis of syphilis, much of the guess-work, incident to treatment and

other matters connected with the disease, has been eradicated and today we are reasonably sure, in the absence of this reaction, that our patient is free therefrom. Bearing in mind that the arsenic compounds are not invariably curative, it is necessary that a course of mercurial treatment be adopted in practically all cases and continued until such time as the Wassermann has been negative for a sufficient time to warrant the knowledge of an absolute cure. In this connection it is suggested that the salicylate of mercury is the best salt to employ, although some favor the succinimide.

It will not be necessary to go into details as to the preparation and use of any of the drugs mentioned as the technique has been so thoroughly discussed elsewhere as to hardly warrant repetition. It goes without saying that all the different agents should be in such shape as to be readily absorbed. Primarily, as was the case with atoxyl and sodium cacodylate, salvarsan was injected intramuscularly but today we find the intravenous application becoming of greater popularity. Some authorities suggest that a dose of from 0.4 to 0.5 grams of salvarsan be administered intravenously to be followed in 48 hours by an intramuscular injection of from 0.3 to 0.4 grams. This should invariably, no matter which method is employed, be followed by regular injections of small doses of mercury salicylate, into the lumbar muscles.

As to the technic, there is but little variance from other hypodermic or intravenous injections. Every antiseptic precaution should be taken, and more especially when the intravenous method is followed. In the latter method some favor the use of the syringe, while others prefer the introduction of the drug by gravity. The latter is possibly the better way in that undue force is not expended in throwing the solution into the vein, as might possibly be the case through use of the syringe. The buttock is the usual site of intramuscular injections and these should be thrown deeply into the tissues. The intravenous method offers the advantage of quicker and more thorough absorption of the drug and is undoubtedly the better procedure.

It is possible, as time goes on, that we will be offered a serum or bacterial vaccine for the treatment of syphilis but thus far none worthy of mention has been offered.

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The hypodermic syringe. 1914

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The hypodermic syringe. 1914

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